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EDITORS
I. A. B. CATHIE and RICHARD H. DOBBS

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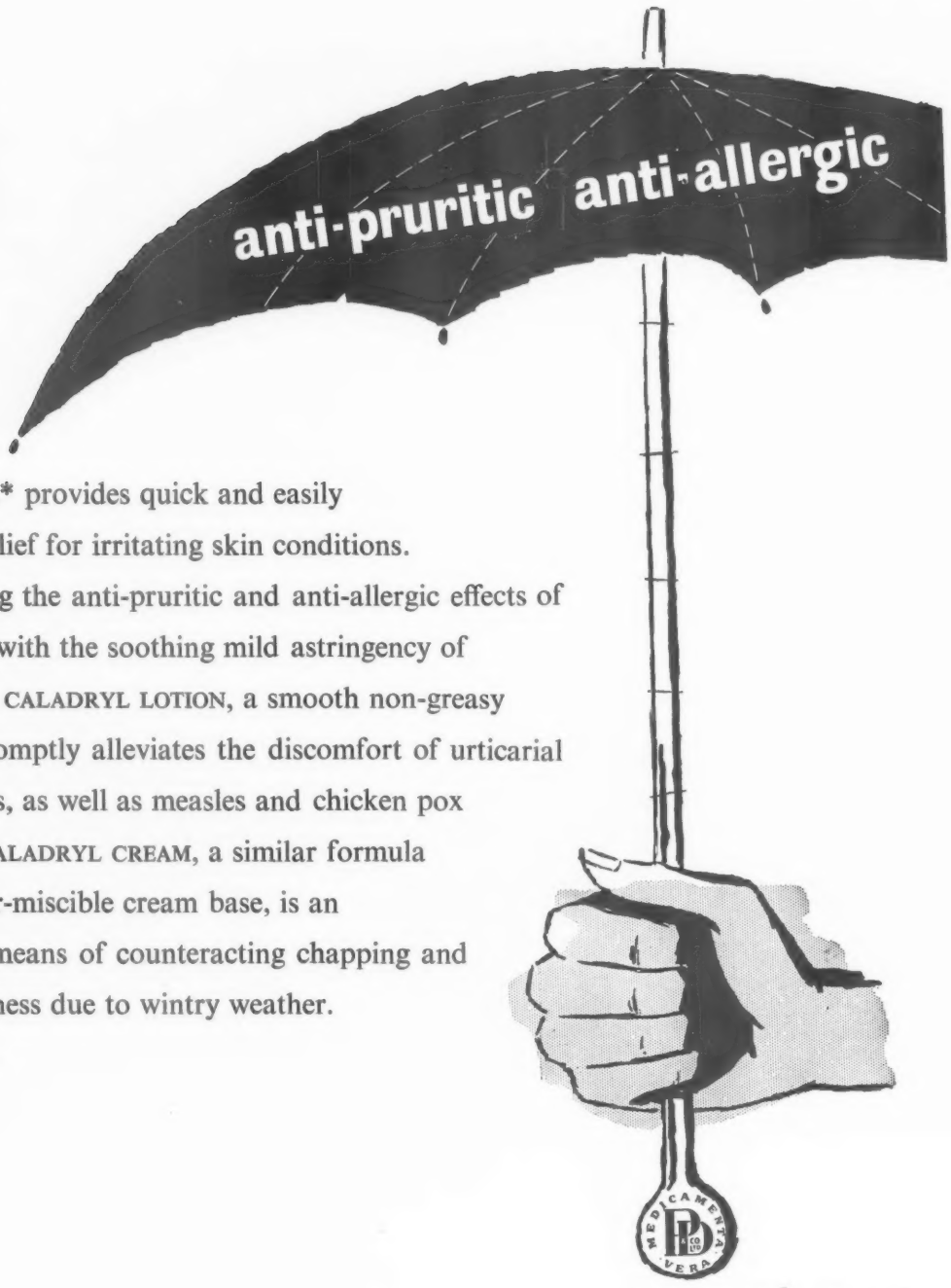

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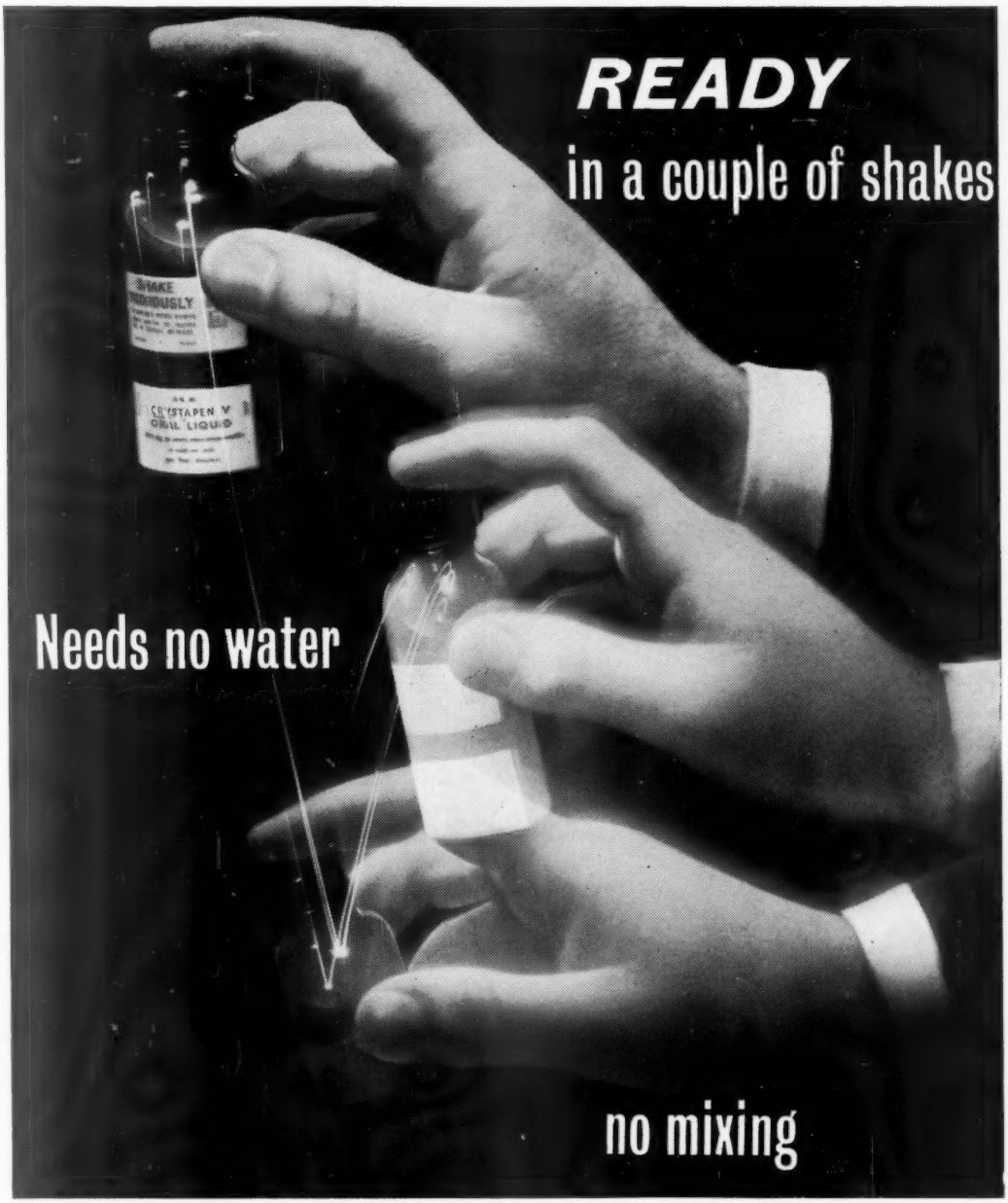

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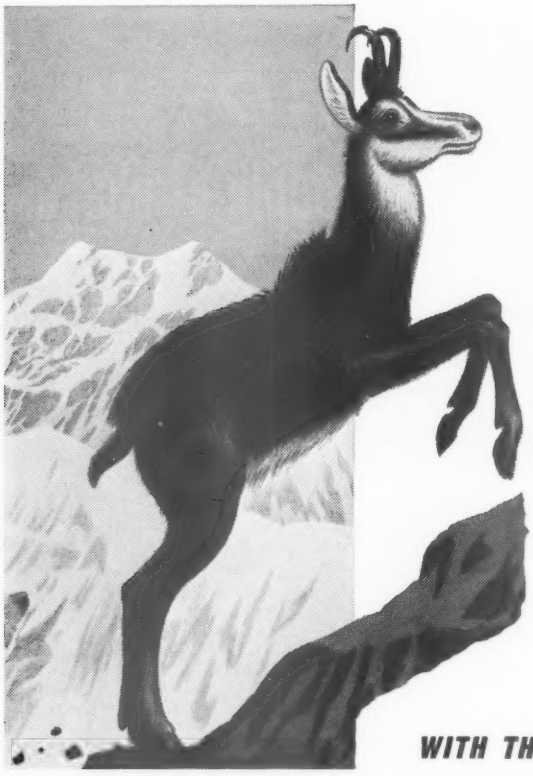

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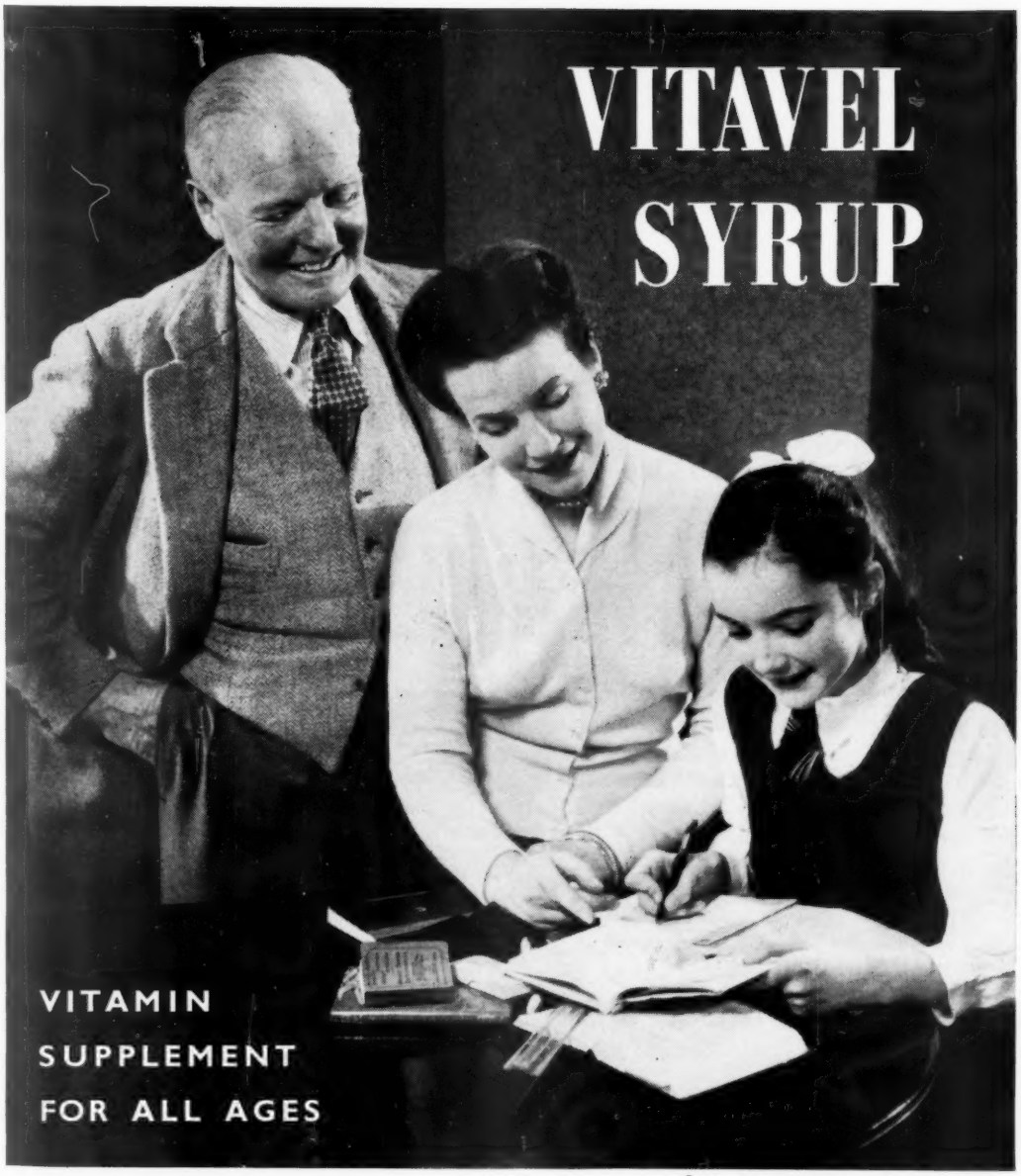

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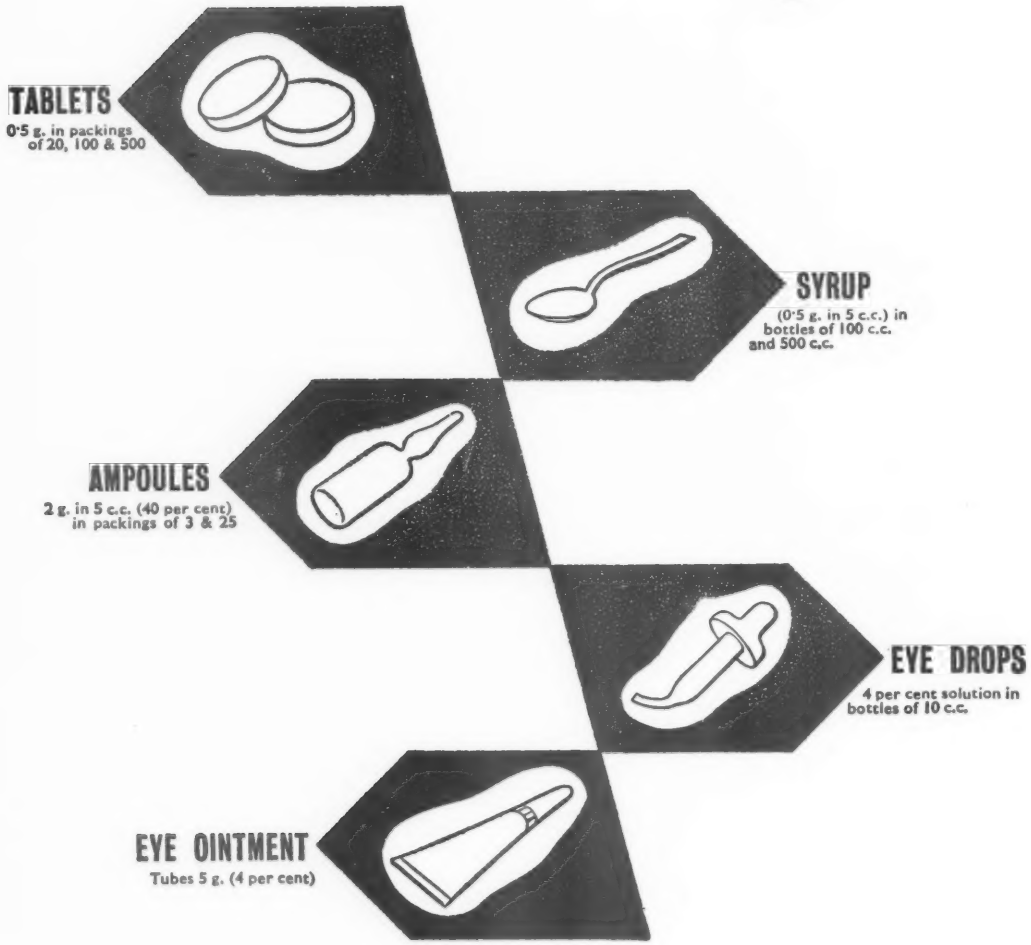
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REGIONAL OBSTRUCTIVE EMPHYSEMA IN INFANCY

BY

JAMES THOMSON and JOHN O. FORFAR

From the Royal Infirmary, Dundee, and the Western General Hospital, Edinburgh, and from the Departments of Child Health, University of St. Andrews and University of Edinburgh

(RECEIVED FOR PUBLICATION JULY 31, 1957)

Over a quarter of a century ago Chevalier Jackson (1930) showed that the bronchi could act as valves in such a way that with respiration a lung or a lobe of a lung could become over-inflated. This valvular action would appear to be dependent on two physiological facts, first that the bronchi dilate on inspiration and contract on expiration (Reinberg, 1925; Heinbecker, 1927; Jackson, 1930), and that inspiration is predominantly an active muscular movement and is consequently more powerful than expiration which is largely a passive recoil. Thus on progressive reduction of the bronchial lumen by any obstruction a point will be reached at which the lumen is closed on expiration but allows air to enter on inspiration due to the greater power of this action and the slight bronchial dilatation which accompanies it. In the adult a functional disorder of this nature appears to be rare; in the infant, possibly due to the narrower bronchial lumen and greater elasticity of the bronchial wall, it can occur much more readily.

In generalized as opposed to regional obstructive emphysema the whole of the lung and both lungs are equally involved in the emphysematous process. Such may be seen in asthma or in acute bronchiolitis of infancy. In regional obstructive emphysema the emphysema is focal in distribution. It is more commonly unilateral but can be bilateral.

Valvular obstruction of the main lobar bronchus produces obstructive lobar emphysema in virtue of the fact that a lung lobe is a sealed self-contained unit (Fig. 1). Obstruction of smaller bronchi and bronchioles will not produce lobular emphysema provided the interalveolar pores (pores of Kohn) remain patent (Van Allen and Soo, 1933). In any segment of a lung less than a lobe these interalveolar pores allow escape of air from the alveoli in the affected segment to alveoli in the unaffected segment and thus prevent over-inflation in the affected segment. If, however, sticky secretions or other material or inflammatory swelling of the interalveolar septa cause obstruction of the interalveolar pores lobular emphysema may occur (Fig. 1). If, too, all the lobular bronchi are equally involved in the obstructive process so that no escape route for air remains, generalized lobular emphysema will result.

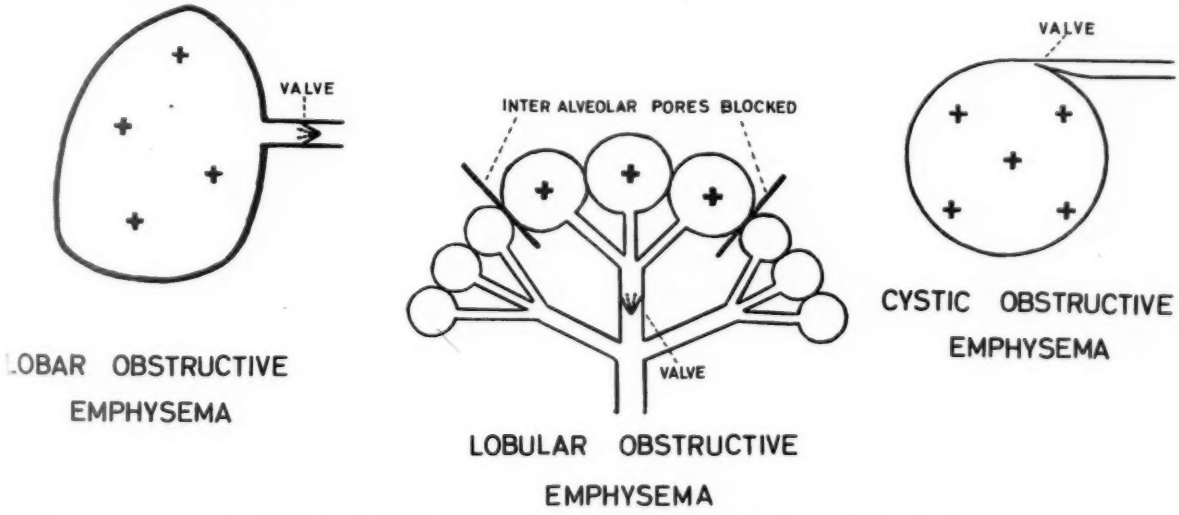

FIG. 1.—Mechanism of production of obstructive emphysema—lobar, lobular and cystic.

We report here a number of cases in which regional obstructive emphysema occurred in infants due to a variety of causes, and we classify the emphysema into three main anatomical types—lobar, lobular and cystic—with subsidiary groupings dependent on the pathogenesis of the condition.

LOBAR OBSTRUCTIVE EMPHYSEMA

Congenital Lobar Emphysema: Presumed Bronchial Obstruction

Case 1. This male infant, born at full term, was admitted to hospital on March 22, 1945, when 10 days old with the history that from the third day he had been having frequent breathless attacks. During these attacks he became cyanosed. Between attacks his breathing appeared normal. His birth had been normal.

On admission to hospital he was noted to be cyanosed and the respiration rate was rapid (60-70 per minute). The respirations were laboured. He had a cough, producing thin mucoid material. The percussion note over the left lung was hyper-resonant and over the right was impaired. On auscultation air entry was much diminished in all areas. The heart sounds were most distinctly heard on the right side of the chest.

Radiological examination revealed gross tension emphysema of the left lung, probably the left upper lobe with secondary collapse of the left lower lobe. The left side of the diaphragm was depressed, the left intercostal spaces widened and the mediastinum was displaced to the right (Fig. 2).

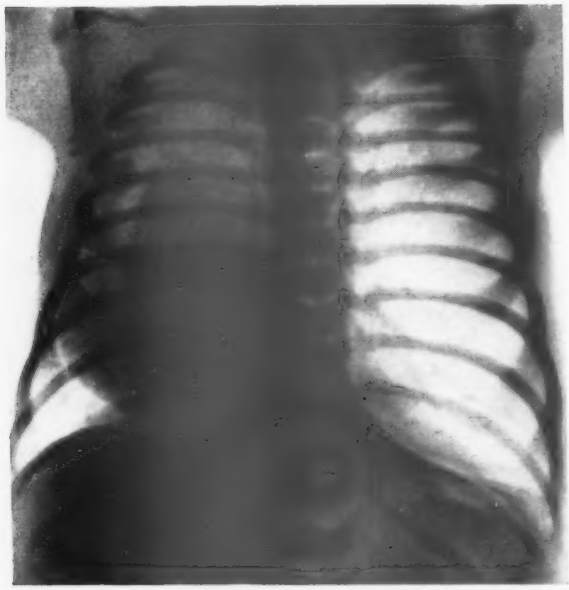

FIG. 2.—Case 1: Congenital lobar emphysema of the left upper lobe.

His condition deteriorated rapidly and he died a few hours after admission. No post-mortem examination was carried out.

Congenital Lobar Emphysema: Presumed Bronchial Obstruction

Case 2. A boy aged 4 weeks was admitted to hospital on September 26, 1955. He was the fourth child, born at full term after an uncomplicated labour lasting four hours. His birth weight was 9 lb. 5 oz. (4,198 g.).

Throughout his stay in a maternity unit his cry had been weak and his respirations noted to be somewhat laboured with accentuated respiratory movements. He was breast fed but required frequent rests during his feeds. He was discharged home on the tenth day.

On the fifteenth day of life he developed a sudden attack of cyanosis in which his lips were described as 'inky'. He held his head back and rolled it continuously from side to side. He did not lose consciousness and after one hour his colour gradually improved.

During the next two weeks he had several similar attacks of 10 to 60 minutes' duration. These bore no relation to feeding. For a week before admission he had a cough.

On admission he was a well-nourished baby with a weak cry. The temperature and pulse rate were normal. The respiration rate was 50 per minute. He had a slight cough and the alae nasi were moving. The chest remained fully expanded in all phases of respiration and the apex beat could not be detected. There was marked indrawing of the lower intercostal spaces and upper abdomen associated with vigorous respiratory efforts. Over the right lung the percussion note was hyper-resonant and over the left it was relatively diminished. The breath sounds were much reduced on the right side and to a lesser extent on the left. Radiological examination showed well-marked obstructive emphysema of the right lung with displacement of the mediastinum to the the left (Fig. 3). The right lower and probably right

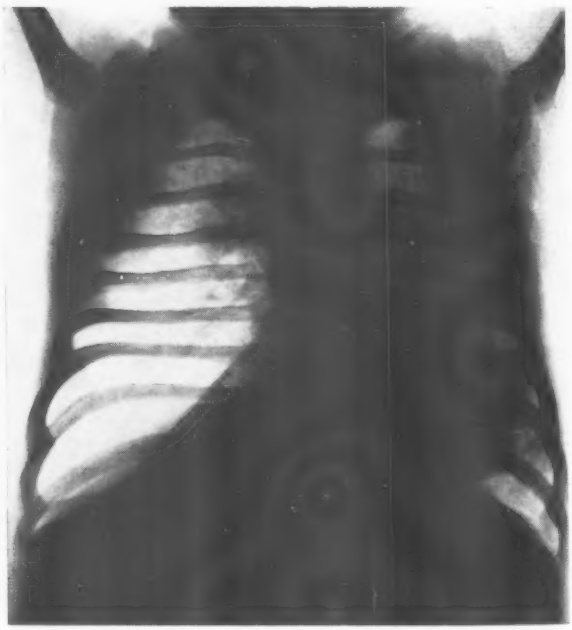

FIG. 3.—Case 2: Congenital lobar emphysema of the middle lobe of the right lung.

upper lobes were subject to pressure collapse, suggesting that it was the middle lobe which was emphysematous. The intradermal tuberculin test was negative up to a strength of 1/1,000.

On the second day after admission he had two brief cyanotic attacks accompanied by marked respiratory embarrassment and a severe degree of cyanosis not immediately relieved by oxygen.

Two days later bronchoscopy (Mr. M. Fallon) was carried out. During induction of anaesthesia and during the operation there was considerable respiratory difficulty. The left bronchus appeared normal. The right showed no evidence of a foreign body, but a bleb of pus was present in it and appeared to be coming from the right upper lobe bronchus.

On the following day he suddenly developed glottic oedema and required an emergency tracheotomy. Frequent suction was maintained through the tracheotomy tube and during this time there was no respiratory embarrassment. Thereafter the tracheotomy wound was allowed to close. When it did so episodic respiratory difficulty returned.

Radiologically right-sided emphysema persisted; paradoxical movement of the mediastinum was not observed but absence of movement of the right side of the diaphragm was evident on screening.

Operative removal of the affected lobe was decided on, and was carried out at the age of 7 weeks. The operation was preceded by paracentesis through the chest wall, and the intrapulmonary pressure within the emphysematous lobe was found to be greater than the 35 cm. of water which was the highest pressure which our manometer could record. The normal pressure at this age is said to be less than 5 cm. of water. Deflation of the emphysematous lung facilitated anaesthesia. At operation the right middle lobe was seen to be grossly distended even in spite of decompression. It was resected. The adjacent lobes re-expanded immediately.

Post-operatively the child made a satisfactory recovery although he subsequently suffered an attack of pneumonia. Apart from that he has remained well over the past 18 months and radiologically the lung fields have remained normal.

Pathological examination of the excised middle lobe (Dr. K. Rhaney) showed that the whole of the right middle lobe was grossly over-inflated. Injected fluid passed freely in and out of the main bronchus. Cartilage in the walls of the bronchus appeared deficient but this may have been due to overdistension, giving a false appearance of disproportion. No mucous membrane folds or aberrant blood vessels likely to cause obstruction were found. Thus no convincing pathological cause for the obstruction could be demonstrated.

The possibility remains that deficiency of cartilage or some obstruction of the portion of the main bronchus not removed at operation was the responsible factor. It is possible also that functional distortion of the bronchus not evident in the excised lobe was present in life and contributed to the valvular obstruction.

Congenital Lobar Emphysema: Presumed Bronchial Obstruction

Case 3. This boy was born on September 3, 1956, some three weeks prematurely by spontaneous vertex delivery, birth weight 6 lb. 2 oz. (2,778 g.). He cried lustily after birth but the hands, feet, and face were cyanosed. A good deal of liquor was aspirated. Oxygen lessened but did not abolish the cyanosis. Some five hours after birth the respirations had become shallow and rapid (approximately 100 per minute). A few hours later there was marked costal margin recession and intercostal indrawing. It was noted that he was less distressed when lying on the right side. At that stage there was some diminution of air entry over the left lung. Radiologically the left lung was only slightly aerated, aeration of the right lower lobe was diminished and it was apparently normal in the right upper lobe. Despite this a lateral view showed anterior bowing of the sternum, suggesting emphysema, and well-marked aeration of the retrosternal space.

Three days later the respiration rate fell suddenly to 50-60 per minute, most of the symptoms disappeared and a chest film showed normal aeration of both lungs. Thereafter over a period of a month there were several episodes of sudden tachypnoea and slight cyanosis, not usually of longer than 15 minutes' duration. Periodic radiological examination showed varying degrees of collapse of the right middle and lower lobes. There was evidence of increased pressure within the right upper lobe with increased density of air, widening of the intercostal spaces and horizontal positioning of the ribs (Fig. 4). On screening the right upper lobe remained

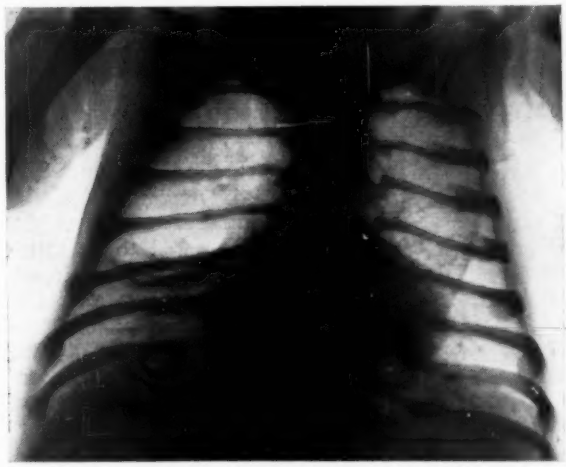

FIG. 4.—Case 3: Obstructive emphysema of the right upper lobe, showing horizontal position of ribs, widened intercostal spaces, and partial collapse of right middle and lower lobes.

inflated on expiration and herniated across the mediastinum (Fig. 5).

At the age of 2 months a bronchogram was carried out. Lipiodol freely entered the collapsed right lower and middle lobes showing no evidence of bronchial obstruction. The right upper lobe bronchus was filled much less satisfactorily despite attempts to accomplish

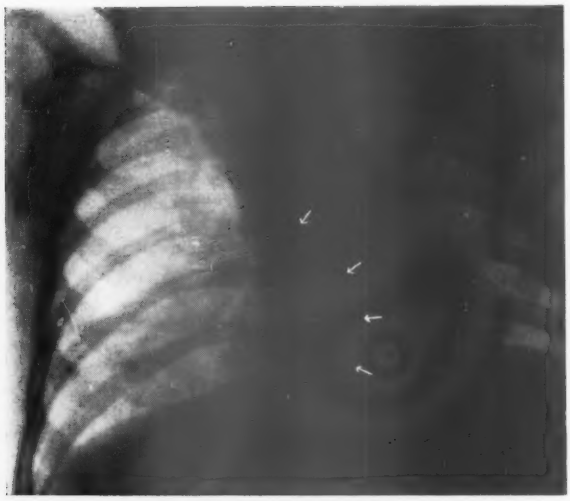

FIG. 5.—Case 3: Obstructive emphysema of the right upper lobe and mediastinal pleural herniation on expiration.

this. At this stage the air entry over the right upper lobe was markedly diminished.

This infant was considered to be suffering from congenital lobar emphysema of the right upper lobe. In the first few days of life this had prevented adequate expansion of the left lung and right lower lobe, presumably due to pressure on them, and latterly had caused pressure collapse of the right lower lobe.

After the age of 1 month his symptoms became less severe and he began to feed well and to gain weight satisfactorily. By the age of a year he was relatively symptom free, although he became severely distressed during an intercurrent respiratory infection. Radiologically there was little change in the lung.

Lobar Obstructive Emphysema : Extrabronchial Compression by an Enlarged Heart

Case 4. This girl had been born at term, birth weight 6 lb. (2,722 g.). Her progress appeared to be satisfactory until she was 9 months old, when she developed cough, anorexia and fretfulness. Five days after the onset of these signs she was admitted to hospital.

At the time of admission, on November 8, 1948, she was relatively symptom free but radiological examination of the chest showed cardiac enlargement with some emphysema of the lower lobe of the right lung. There were no cardiac murmurs. Two days after admission there occurred a sudden incident of respiratory embarrassment when her respiration rate rose to 80 per minute, and the percussion note over the right lung became hyper-resonant as compared with the left. These signs disappeared after a few hours. For 10 days she remained well then developed, quite suddenly, a further episode of tachypnoea with respiratory distress. Clinically the heart was displaced to the left and there was intercostal indrawing. Radiological examination after the worst of her symptoms had passed off showed tension emphysema of the right middle and lower lobes (Fig. 6). A lateral film showed the trachea displaced backwards by the enlarged heart (Fig. 7).

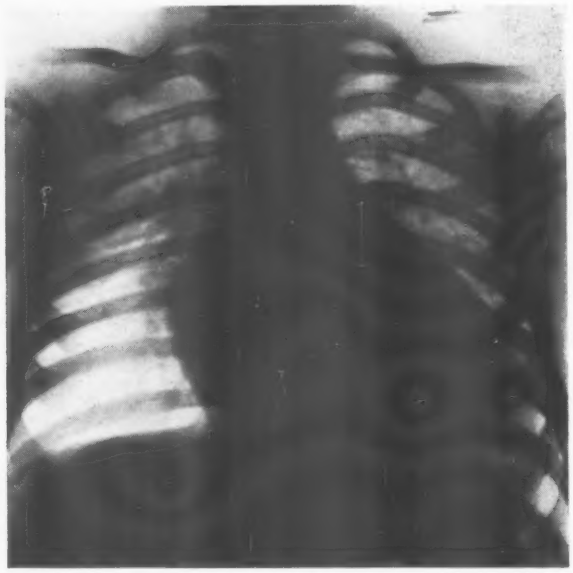

FIG. 6.—Case 4: Enlarged heart and obstructive emphysema of the right lower lobe.

FIG. 7.—Case 4: Enlarged heart and backward displacement of the trachea (normally parallel with the vertebral column).

Over the next few weeks a minor degree of emphysema of the right middle and lower lobes persisted. Finally the left lung collapsed suddenly and completely causing gross respiratory distress and she died 24 hours later.

At post-mortem examination the heart was enlarged 75% above the normal weight for this age. There were no valvular or septal defects. Unfortunately the heart was not examined histologically. The left lung was collapsed due to the pressure of the large heart on the left bronchus. The right lower lobe bronchus appeared liable to pressure from the same cause. There was emphysema of the right middle and lower lobes with partial collapse of the right upper lobe. Histological examination of the lungs confirmed the macroscopic findings.

Thus external pressure on the right lower lobe bronchus appeared to be the mechanism producing tension emphysema in this case.

Lobar Obstructive Emphysema : Extrabronchial Compression by Enlarged Glands and Bronchial Obstruction by Mucopus

Case 5. This boy, whose birth weight was 6½ lb. (2,948 g.), was a first child of a British mother and an Indian father. There was no family history of tuberculosis. At the age of 4½ months he was admitted urgently to hospital. For 11 days he had had a cough and wheezy respiration, and a few hours before admission to hospital he had become remarkably breathless and restless.

On admission on September 6, 1948, he showed well-marked respiratory distress with intercostal indrawing and a respiration rate ranging from 40 to 60 per minute. The chest remained in the position of full inspiration. After a few hours his symptoms passed off but returned on the following day when there was diminished air entry over the lower lobe of the right lung with fullness of the right side of the chest. The percussion note over the right lung was resonant.

Radiological examination showed marked tension emphysema of the middle and lower lobes of the right lung, cardiac displacement to the left, depression of the right diaphragm, increase in the width of the intercostal spaces, upward displacement of the interlobar fissure and a mediastinal pleural hernia (Fig. 8). Radiological examination three days later when his acute symptoms had abated showed that the tension emphysema in the right lung had greatly diminished.

Over the ensuing weeks there was a progressive infiltration into the right lung with hilar gland enlargement. Bronchoscopy was carried out six weeks after admission. No foreign body was seen. A considerable amount of thick, sticky secretion was present in the right main bronchus and the mucosa was swollen, but no blockage could be detected. The left bronchus appeared normal. Two days after bronchoscopy a tension pneumothorax developed on the right side of the chest. This was relieved by removing 200 ml. of air which was under considerable pressure. A week later he again developed a tension pneumothorax which, on this occasion, was accompanied by gross surgical emphysema extending from the neck to the lower limbs, and he died a few days later. The intradermal tuberculin test had been negative up to 1/100 on two occasions a month apart.

At post-mortem examination there was mucopurulent secretion in the right lower lobe bronchus. A cavity was present at the right hilum but it was impossible to tell whether this was a liquefied lymph gland or a cavity in lung tissue. There was a septic bronchopneumonia with multiple abscess formation in the right lower lobe. There was also a cavity in the dorsal segment of the right lower lobe. The right lower lobe was covered with a fibrinopurulent layer and the remainder of the lung was adherent to the chest wall. Histological examination revealed a widespread tuberculous infection of the right lung and infection was also demonstrated in the left lung.

The mechanism producing the tension emphysema in this case appears likely to have been a combination of extrabronchial compression by tuberculous glands and intrabronchial obstruction by mucopurulent secretions. The latter appears to be the factor which precipitated the emphysema and which accounted for its sudden onset and disappearance.

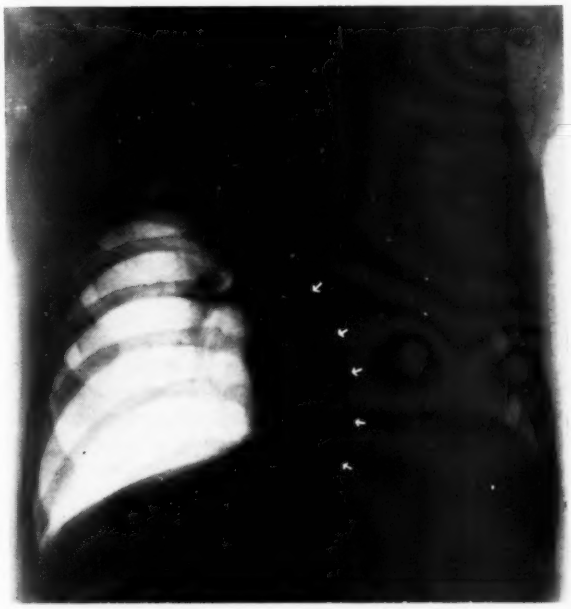

FIG. 8.—Case 5: Obstructive emphysema of the right lower lobe.

Lobar Obstructive Emphysema : Bronchial Obstruction by Mucopus

Case 6. This boy was born at home, birth weight 6 lb. 12 oz. (3,062 g.). He made satisfactory progress for the first four weeks. Five days before admission to hospital he developed an upper respiratory tract infection. Just before admission respiratory symptoms became much more marked with cough, cyanosis and increasing dyspnoea.

On admission on February 13, 1957, his temperature was 101° F. and his respiration rate 60 per minute. There was indrawing of the intercostal spaces and costal margin recession. The left side of the chest was fuller than the right. Coarse crepitations were audible over both lungs, especially the right. Cyanosis was evident and responded to oxygen. The white cell count was 14,000 per c.mm.

Radiological examination showed obstructive emphysema involving the left lung with some displacement of the mediastinum to the right and slight mediastinal pleural herniation, increased aeration of the left lung with widening of the intercostal spaces and depression of the diaphragm (Fig. 9). The right lung showed secondary collapse with patchy consolidation.

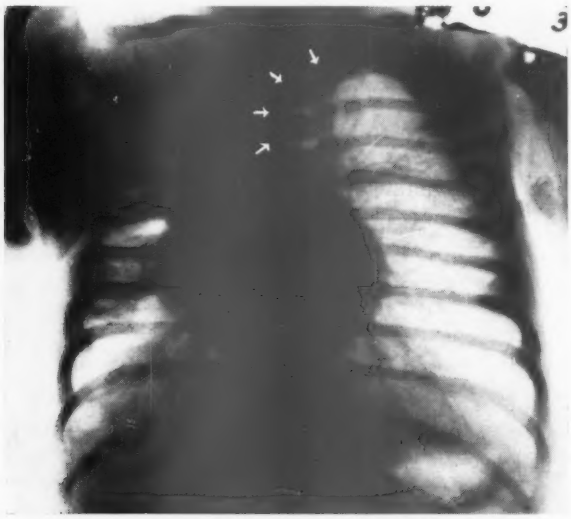

FIG. 9.—Case 6: Obstructive emphysema of the left lung, mediastinal displacement, partial collapse and consolidation of the right lung.

After 48 hours' treatment with penicillin and streptomycin most of his symptoms had disappeared, his temperature had become normal and radiographs of the chest showed that obstructive emphysema was no longer present, the lungs showing only minor inflammatory change.

He made an uninterrupted recovery. It appears likely that the obstructive emphysema of the left lung resulted from obstruction of the left main bronchus with mucopus in an infant suffering from pneumonia.

LOBULAR OBSTRUCTIVE EMPHYSEMA

Lobular Obstructive Emphysema : Aspiration of Mucus and Spontaneous Pneumothorax

Case 7. This boy was born at term on October 14 1956. He was very 'mucousy' at birth and was asphyxiated. He was given intragastric oxygen. He remained cyanosed and respiratory movement was accentuated. Crepitations were audible over both lungs. Radiological examination just after birth showed patchy atelectasis throughout both lungs with an area of obstructive

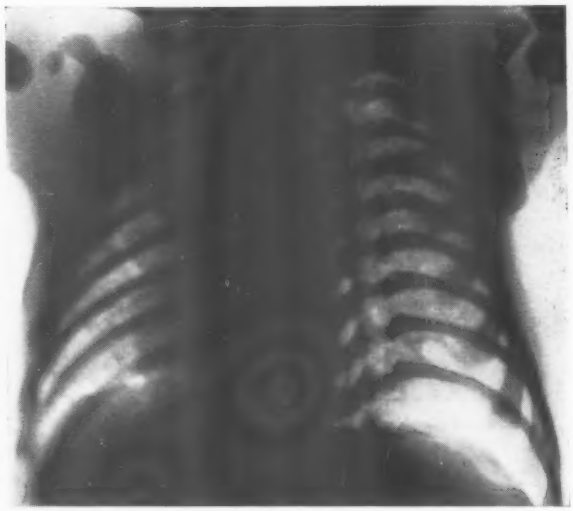

FIG. 10.—Case 7: Lobular obstructive emphysema of the left lower lobe.

emphysema at the left lung base (Fig. 10). Respiratory embarrassment continued and a second radiograph seven hours after the first showed a pneumothorax on the left side. Paracentesis of the left pleural cavity produced a few millilitres of air with some diminution of respiratory distress. On the following day marked respiratory embarrassment recurred and was relieved by aspirating the pleural cavity, when 20 ml. of air under considerably increased pressure were removed. Again there was marked clinical improvement. A few hours later the chest had again to be tapped. Over the next 24 hours his respiratory difficulty progressively diminished and the crepitations which had persisted from birth gradually disappeared. He made a satisfactory recovery and two days after birth there was no longer radiological evidence of pneumothorax.

Aspiration of mucus into the lungs in this case appeared to have produced obstructive emphysema involving particularly the lower lobe of the left lung. Air had ruptured into the pleural cavity from the over-distended left lung causing a pneumothorax.

Lobular Obstructive Emphysema : Aspiration of Mucus

Case 8. This boy was born at term on April 14, 1956, by spontaneous vertex delivery, the birth weight being 6 lb. 3 oz. (2,806 g.). He was very 'mucousy' at birth. Twelve hours after birth moderate respiratory difficulty was still present, the costal margin receding on inspiration and the anterior chest wall bulging forward. Radiological examination showed hyperaeration of the lungs, particu-

larly on the left side with splaying and horizontal positioning of the ribs, depression of the diaphragm and some mediastinal displacement to the right (Fig. 11).

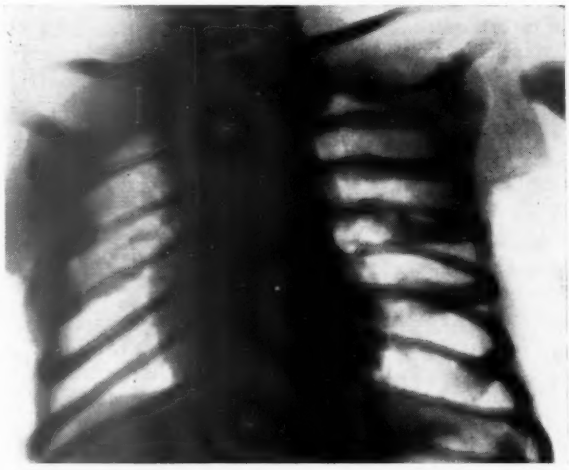

FIG. 11.—Case 8: Obstructive emphysema, especially of the left lung, widening of the rib spaces and slight mediastinal displacement.

A few days later all abnormal physical and radiological signs in the chest had disappeared.

In this case, consequent on aspiration of mucus, there appeared to be widespread tension emphysema with the left lung more affected than the right.

Lobular Obstructive Emphysema : Aspiration of Vomitus

Case 9. This boy was born at term, the birth weight being 7 lb. 4 oz. (3,289 g.). At the age of 11 weeks he developed an acute episode of vomiting. A few hours after the onset of this he was found in his cot collapsed and in obvious respiratory distress. He was admitted to hospital on May 9, 1956, exhibiting marked bronchospasm and with the chest fully inflated. He died shortly after admission.

Post-mortem examination (Dr. K. Rhaney) showed aspirated vomit throughout most of the bronchial tree, even to the smallest respiratory passages. Most of the lung tissue was acutely over-distended with air and the lungs did not collapse on opening the chest. Histological examination confirmed the emphysema of the lungs and showed no evidence of acute inflammation.

No doubt in this case the vomitus blocked the bronchi in such a way as to obstruct outflow of air but allowed some entry of air on inspiration.

CYSTIC OBSTRUCTIVE EMPHYSEMA

Cystic Obstructive Emphysema : Congenital or Acquired Cyst

Case 10. This boy was born six weeks prematurely on March 4, 1955, the birth weight being 3 lb. 12 oz. (1,701 g.). He fed poorly from birth but apart from that remained reasonably well for two weeks when he developed gastro-enteritis. This illness was complicated by pneumonia. Two weeks later he suffered a second attack of pneumonia from which he again made a satisfactory recovery.

At the age of 3½ months he had a third attack of pneumonia accompanied by a febrile convulsion, and was admitted to hospital. Radiological examination showed an air-containing cyst in the left lung in the posterior basal segment of the lower lobe (Fig. 12).

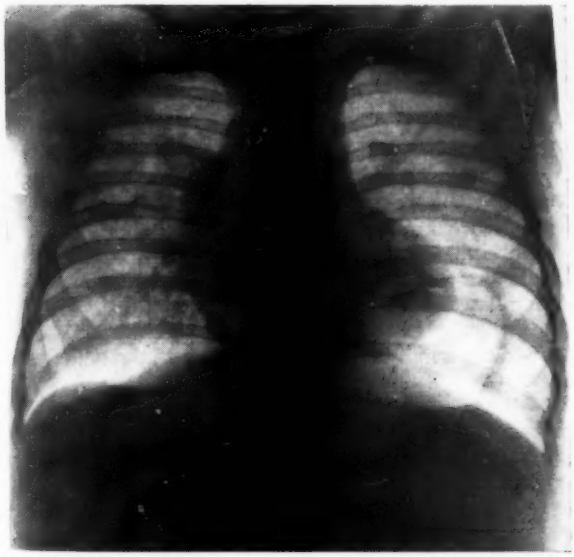

FIG. 12.—Case 10: Congenital or acquired cyst of the left lower lobe.

Clinically he was noted to be intermittently dyspnoeic, particularly on sitting up. The intercostal spaces were markedly indrawn and the costal margin receded on respiration. He had a persistent cough.

Intermittent respiratory embarrassment and indrawing of the chest persisted for four months. The cyst remained unaltered and it was decided to remove it. At operation on November 16, the lower lobe was found to be adherent to the paravertebral gutter and the diaphragm. The lung was freed and the lower lobe was found to contain a large cyst with collapse of surrounding lung tissue. The cyst was removed by resection (Mr. M. Fallon).

On recovery the remainder of the left lung expanded fully, and over a period of a fortnight all abnormal signs disappeared from the chest, except some costal indrawing.

On pathological examination (Dr. K. Rhaney) the cyst was found to be surrounded by lung tissue. A bronchus entered the cyst from the supero-medial aspect, running obliquely through the wall and entering the cavity under a crescentic valve-like fold in the external lining. Macroscopically there was no evidence of pneumonia. Histologically the cyst was found to be of bronchial origin, lined by pseudo-stratified ciliated columnar epithelium.

Deep to the epithelium were bundles of smooth muscle fibres forming a complete layer round the cyst. A bar of cartilage was present in the cyst wall, the surrounding lung was collapsed, and in the hilar region there was some chronic inflammatory change.

It would be difficult to say whether this cyst was congenital and predisposed to recurrent pneumonia or whether it was the result of the attacks of pneumonia. The mechanism whereby it persisted seems clear, however, namely the valvular entry of the bronchus into its wall.

Cystic Obstructive Emphysema : Post-pneumonic Pneumatocoeles

Case 11. This girl was the third child of healthy parents. She was born at full term on May 7, 1953, her birth weight being 7 lb. 13 oz. (3,544 g.). On the second day she began to vomit and on the fourth day the vomitus was slightly bloodstained. An oesophageal hiatus hernia was suspected and on the sixth day a 'lipiodol' swallow was given. This showed that an oesophageal hiatus hernia was present, but during the examination some 'lipiodol' was aspirated into the lungs with the result that inadvertently bronchography was carried out. This showed a normal bronchial tree and the lung fields were clear.

She was nursed in the upright position and the vomiting lessened. She was discharged home on the 23rd day gaining weight satisfactorily. Eight days later she was readmitted to hospital. For the previous few days the vomiting had increased, she had become fevered and her respirations had become grunting and rapid. Physical examination showed a marked impairment of the percussion note over the upper half of the left lung, coarse crepitations over the posterior aspect of the left lung and some mediastinal displacement to the right. The white cell count was 27,000/c.mm. Radiological examination of the chest showed consolidation of the left upper lobe with early formation of multiple bullae. She was given penicillin intramuscularly, 100,000 units four-hourly, and streptomycin, 0·25 g. six-hourly. After two days her condition remained unchanged and on this account she was given oxytetracycline, 50 mg. six-hourly by mouth, in place of the other antibiotics. From sputum obtained by a cough swab coagulase-positive staphylococci were cultured. The diagnosis made was that of staphylococcal pneumonia involving predominantly the upper lobe of the left lung.

Clinically she responded satisfactorily to oxytetracycline therapy but serial radiological examination showed the development of large emphysematous bullae within the substance of the left upper lobe. Over a period of several weeks these progressively increased in size showing evidence of positive pressure (Fig. 13). She developed an obvious asymmetry of the chest with ballooning of the upper part of the left thorax anteriorly, diminished respiratory movement on that side and costal margin recession. On percussion the area of deep cardiac dullness was absent. There was diminished air entry over the left lung.

This infant continued to be nursed in the upright position and despite the large bullae made very satisfactory progress with a normal weight gain and no cough. Her respiration rate varied between 30 and 70 per minute. The bullae persisted unchanged for a period of nine months. At the end of that time they began to diminish in size and disappeared entirely over a period of two months. She has remained well since, over a period of two years, and has had no further respiratory symptoms. The chest radiograph remains quite clear.

Combined Cystic Obstructive Emphysema and Lobar Obstructive Emphysema

Case 12. A boy, the third child of healthy parents, weighed 6 lb. 1 oz. (2,750 g.) at birth. The birth had been normal at full term and there had been no post-natal asphyxia or respiratory difficulties.

When 7 weeks old he suffered from bronchitis and a week later was admitted to an infectious diseases hospital with gastro-enteritis. He was in hospital for three and a half weeks due to slow recovery and poor weight gain. During his stay in hospital his respiration rate rose suddenly one day to 80 per minute, remained at 50 to 80 per minute for two days and then returned to normal. This incident was accompanied by marked tachycardia.

On June 24, 1949, at the age of 6 months, he was admitted to hospital, having been vomiting for three days. He was noted to be only 50% of the expected weight but no respiratory signs were evident. During the first week his respiration rate was occasionally a little rapid. On the tenth day, following a feed, he developed marked tachypnoea accompanied by respiratory distress. At the same time there was an obvious fullness of the right side of the chest compared with the left; there was a hyperresonant percussion note over the right chest anteriorly and there was marked lower intercostal and costal margin recession, the thoracic cage staying fixed in the position of full inspiration. The breath sounds were diminished over the right lung and the apex beat was

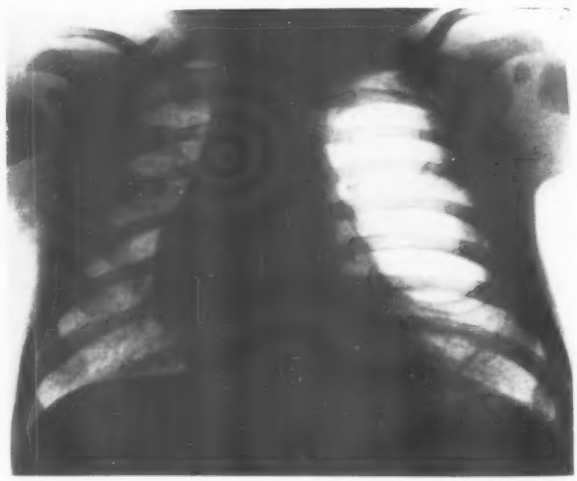

FIG. 13.—Case 11: Fully developed post-pneumonic (staphylococcal) pneumatocoele.

displaced to the left half an inch outside the mid-clavicular line. There was no cough or asthmatoid wheeze. The intradermal tuberculin test was negative up to a strength of 1/1,000. Radiological examination confirmed the presence of obstructive emphysema of the right lung with abnormal radiotranslucency, herniation of the mediastinal pleura into the left hemithorax, cardiac displacement to the left, paradoxical movement of the mediastinum and diminished movement of the right diaphragm (Fig. 14). There appeared to be two air-

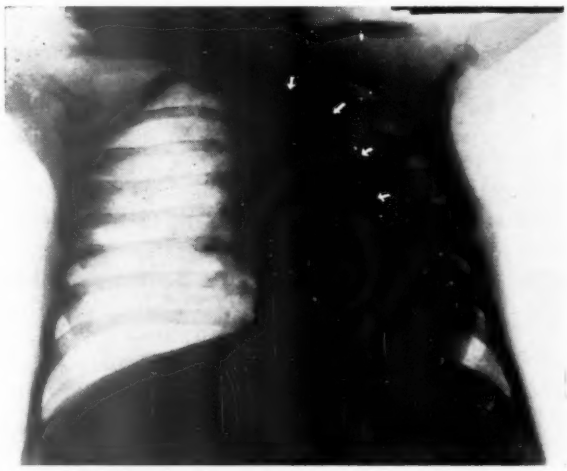

FIG. 14.—Case 12: Obstructive emphysema of the right lung with mediastinal pleural herniation.

containing cysts at the region of the right hilum. Thereafter tachypnoea (50 to 100 per minute) and respiratory embarrassment remained constant.

A few days later bronchoscopy was carried out (Mr. M. J. Gibson). The lumen of the right main bronchus was seen to be moon-shaped, apparently as a result of external pressure. Thereafter dyspnoea became progressively worse, the child's condition deteriorated and he died three weeks after admission to hospital.

At post-mortem examination (Dr. A. B. Goodall) the right lung was voluminous and occupied the whole of the right half of the thoracic cavity and part of the left half, its left anterior border being 2 cm. to the left of the midline. The heart was displaced to the left, the right border of the heart being to the left of the midline. The left lung appeared small and compressed towards the posterior chest wall. The heart was normal and the ductus arteriosus closed. The innominate artery was very short and the right common carotid and subclavian arteries sprang almost directly from the aorta. The bronchial and intercostal arteries appeared to originate normally. A multilocular mucous cyst was present in the superior mediastinum on the left side behind the oesophagus and the trachea, the largest loculus of this cyst being about half an inch in diameter. On section the gross emphysema of the right lung was confirmed. There was no differentiation of the lung into lobes. At the hilar region within the lung substance there was a cyst $\frac{1}{2}$ in. in diameter and immediately above it a smaller cyst about half this size. These cysts were in close relationship to the right main bronchus, the bronchus passing across the posterior wall of the main cyst in its upper aspect. The cysts contained air. Inflation of the right main bronchus caused air bubbles to appear at a slit-like opening in the antero-lateral wall of the larger cyst. This opening was covered by a flap and the obliquity of the track into the cyst was such that the flap acted as a valve preventing egress of air from the cyst. The left lung was not normally lobulated and there was only a rudimentary interlobar fissure. Lymph nodes were not enlarged.

The spleen weighed 4 g. and the liver 170 g. The left kidney weighed 23 g. and there was a normal left ureter. The right kidney and right ureter were absent. The right renal artery was also absent and there was no right ureteric orifice in the bladder. The pancreas appeared normal.

In this case there appeared to be a double valvular mechanism: an air-containing tension cyst at the hilum exerting pressure on the right main bronchus in such a way that valvular emphysema of the lung resulted.

Discussion

These cases are fairly gross examples of regional obstructive emphysema in infancy and illustrate a variety of pathological conditions in which this disorder may occur.

The classification suggested might be represented schematically in the following way:

REGIONAL OBSTRUCTIVE EMPHYSEMA

Lobar		Lobular		Cystic
Congenital lobar emphysema		Liquor amnii Mucus Mucosal swelling Vomitus	producing bronchiolar obstruction in a regional distribution	Congenital tension cysts Acquired (post-pneumonic) cysts
Foreign body Mucus or mucopus Mucosal swelling Granulation tissue	Intra-bronchial			
Enlarged hilar glands Enlarged heart Extra-bronchial cysts Aberrant blood vessels including ductus arteriosus	Extra bronchial			
Mixed Forms				

It is not suggested that every cause of regional obstructive emphysema is mentioned in the above classification but this classification could probably include within it all forms of regional obstructive emphysema whatever the cause.

Diagnosis

Clinically marked obstructive emphysema is likely to be associated with a bulging or 'blown' chest wall, with a resonant or hyper-resonant percussion note and with diminished air entry over the affected region. There may also be signs of mediastinal displacement and loss of cardiac dullness.

Radiologically obstructive emphysema is most likely to be confused with collapse associated with compensatory emphysema. In obstructive emphysema there is essentially evidence of positive pressure over-inflation of the affected part of the lung so that in grosser degrees there may be downward depression of the diaphragm, splaying of the ribs, anterior bowing of the sternum, mediastinal shift, mediastinal pleural herniation and paradoxical movement of the mediastinum on breathing. In Cases 2, 3 and 5 obstructive emphysema of one lobe was associated with secondary pressure collapse of the adjacent lobe. It is important that such a secondary collapse due to external pressure should be differentiated from primary collapse due to bronchial obstruction and accompanied possibly by some compensatory emphysema. As Robertson and James (1951) have pointed out, primary collapse, in contradistinction to secondary pressure collapse, is associated with elevation rather than depression of the diaphragm, and with a greater degree of radio-opacity than a lobe subject to compression by an adjacent emphysematous lobe. The degree of emphysema in compensatory emphysema is at most only slight. Nor is compensatory emphysema ever associated with the ballooning and mediastinal herniation of obstructive emphysema. It seems to us that the radiological diagnosis of compensatory emphysema is made too often in infancy and childhood on the analogy of adult experience and without sufficient regard to the likelihood of obstructive emphysema at this age and to the factors which indicate its presence.

In its lesser degrees, obstructive emphysema may be difficult to demonstrate radiologically. The contrast between normal and emphysematous lung in regional obstructive emphysema does, however, make recognition easier then in generalized emphysema.

As obstructive emphysema is a functional condition dependent on active respiration, lungs affected by it may return to normal size after respiration ceases, and if the degree of over-inflation has been insufficient to exceed the elastic limit of the lung no abnormality may be revealed at necropsy (Carter, 1940).

General Role of Obstructive Emphysema in Producing Respiratory Symptoms in Infancy

Obstructive emphysema may be a much commoner factor in the genesis of respiratory embarrassment in infancy than is generally realized. Because of the difficulty of recognizing it in its minor degrees and at post-mortem examination, the significant role which it may play in respiratory disease in infancy may have been underestimated.

The extent of respiratory distress is no doubt proportional to the volume of lung affected by the emphysematous process and to the severity of the air tension within the lung. It may be, too, that abnormal pressure changes in the lung disturb the neurological control of respiration by virtue of stimuli transmitted via the vagus nerve in the manner of the Hering-Brauer reflex.

Particularly is obstructive emphysema likely to be of importance in the newborn infant and in the infant with respiratory infection. In the newborn, inhalation of mucus and liquor is so common that it would be surprising if widespread lobular obstructive emphysema did not frequently occur. It appears likely that spontaneous pneumothorax in the newborn infant, as seen in Case 6, results from such a mechanism (Silver, 1939). Davis and Stevens (1930) have demonstrated the presence of pneumothorax radiologically in almost 1% of 702 consecutive newborn babies and Solis-Cohen and Bruck (1934) in approximately 2% of 500 neonates. A much higher proportion must surely develop obstructive emphysema without going on to pneumothorax. Where spontaneous pneumothorax develops there are two possible routes by which the air can reach the pleural cavity from the pulmonary alveoli. It may rupture directly through the visceral pleura of the lung, or it may travel indirectly, rupturing first into the interstitial tissue (Howie and Weed, 1957), tracking thence to the root of the lung (Macklin, 1939) and rupturing through the mediastinal pleura which yields more easily than does the visceral pleura (Hamman, 1939). The latter appears to be the common route. In infection, too, conditions predisposing to obstructive emphysema are likely to be present. Inflammatory swelling and secretions are likely to block the interalveolar pores and the smaller bronchi and bronchioles are likely to be partially obstructed by swelling of their lining mucosa and by inflammatory exudate. From the clinical point of view the over-inflation and bulging of the thoracic cage and the hyper-resonant percussion note seen frequently in respiratory infection in infants are in keeping with the view that in such cases obstructive emphysema is a common and significant cause of disordered respiratory function.

Acute bronchiolitis, in particular, creates conditions favourable for the occurrence of generalized obstructive emphysema (Nelson and Smith, 1945).

In the adult, in contradistinction, obstructive emphysema appears to be an uncommon occurrence, although it has been reported to have resulted from mucous plugs and from carcinoma obstructing the main bronchi (Maxwell, 1940). The infant seems to be much more prone to it and the narrow lumen of the bronchi and greater elasticity of the bronchial walls may be relevant factors. During the period of infancy, too, congenital anomalies of the bronchi are likely to reveal themselves. The possibility of their occurrence should be borne in mind in any infant who exhibits episodic tachypnoea, intercostal indrawing or respiratory embarrassment.

Lobar Obstructive Emphysema

Although in some cases of lobar emphysema, as for example with a foreign body, the check-valve mechanism described by Jackson is clearly evident this is not always so.

In congenital lobar emphysema no obvious valvular mechanism may be evident (White-Jones and Temple, 1954; Holzell, Bennett and Vaughan, 1956). In other cases deficiency of the cartilaginous rings of the bronchial wall similar to that seen in Case 1 has been described (Overstreet, 1939; Fischer, Tropea and Bailey, 1943; Shaw, 1952) and it is postulated that in these undue flaccidity of the bronchial wall allows it to collapse or become distorted during expiration in such a way as to cause obstruction to the egress of air. An association between mucous membrane folds and deficient bronchial cartilage has been reported (Fischer *et al.*, 1952) and mucosal folds alone have been held responsible for obstructive emphysema (Robertson and James, 1951). External pressure on a bronchus by an aberrant artery and by a patent ductus arteriosus has been reported (Robertson and James, 1951; Fischer *et al.*, 1952). Clark, Nairn and Gowar (1956) have brought forward evidence that congenital bronchostenosis may occur and act as a check valve. The bronchial obstruction which in Case 11 resulted from external pressure by a congenital cyst which was itself subject to obstructive emphysema appears to be a unique mechanism.

In congenital lobar emphysema symptoms of dyspnoea, tachypnoea and cyanosis may be present from birth. Frequently they develop or recur within a few days or weeks of birth. Distress may be acute and early recognition may be life saving.

Barsby (1941) reported three cases of obstructive emphysema resulting from pressure by tuberculous hilar glands, and at that time could find only 16 other reports of this condition in the literature. The majority of cases occurred during the first year of life.

Whether or not operative treatment is employed in lobar obstructive emphysema must depend on the cause and nature of the valvular mechanism and the severity of the emphysema. In Case 1, not operated on, congenital lobar emphysema proved rapidly fatal. In Case 2 operative treatment was successful. In Case 3 spontaneous recovery seems likely. Several reports on the value of resection of affected lobes in congenital lobar emphysema have appeared (Leahy and Butsch, 1949; Robertson and James, 1951; Williams, 1952; Fischer *et al.*, 1952; Holzel *et al.*, 1956). Sloan (1953), however, reported four patients who had residual symptoms after lobectomy. Two of these showed radiological evidence of the further development of emphysema in other parts of the lung following operation. Cases of congenital lobar emphysema can recover spontaneously (Caffey, 1953; Holzel *et al.*, 1956). Holzel *et al.* have described a child with congenital lobar emphysema showing symptoms from birth and not operated on who gradually improved as he grew older. At 5 years of age he was in good health and radiologically there was minimal evidence of emphysema. Thus, although resection of the affected lobe in congenital lobar emphysema may be a life-saving measure and is probably indicated in severe cases, it does not follow that operation should be invariably undertaken. The extent and frequency of respiratory embarrassment will probably be the determining factors. Deflation of the lung can be carried out as an immediately pre-operative measure by the introduction of a needle through the chest wall, and in acute respiratory embarrassment this may be a necessary emergency procedure. Although we used this procedure successfully in Case 2 it has not always been found to be of benefit.

In the acquired forms of lobar obstructive emphysema except for that produced by foreign bodies there is probably less scope for operative treatment. A foreign body in a bronchus which cannot be dislodged by coughing or posturing is a clear indication for bronchoscopic removal. Tuberculous granulation tissue which can be clearly visualized on bronchoscopy and which is causing respiratory distress in virtue of obstructive emphysema should probably be removed (Graham and Hutchison, 1947). Thoracotomy for the removal of tuberculous hilar glands exerting pressure on bronchi and causing severe obstructive emphysema may be an operative emergency (Macpherson, 1957). Where, as in Case 6, mucopus and swelling of the mucous membrane are responsible for obstruction, appropriate antibiotic therapy will be the most important factor in treatment.

Lobular Obstructive Emphysema

Considering the various types of emphysema quantitatively, lobular emphysema is almost certainly the most commonly occurring for the reason that aspiration into the lungs in the newborn and infection and bronchospasm in infancy are so common. When severe and massive the clinical features of pulmonary over-inflation resulting from lobular emphysema may be obvious enough. In its lesser forms, however, lobular obstructive emphysema may be less evident clinically. Yet arguing by analogy from the severe generalized lobular obstructive emphysema seen in acute bronchiolitis of infancy and from the severe regional lobular obstructive emphysema present in cases such as 7 and 9 reported here, it is likely that any obstruction of smaller bronchi or bronchioles in infancy by aspirated fluid, secretions, or swelling of the lining mucosa may result in lobular emphysema of varying degree. The development of obstructive emphysema in any lobule is likely to interfere to a greater or lesser extent with its functional capacity.

Cystic Obstructive Emphysema

Conway (1951) has described varieties of lung cyst and discussed the aetiology in the light of the cases which he reported and the literature on the subject. He accepts that congenital cysts can undoubtedly occur but concludes that the majority of lung cysts seen after the first few days of life are acquired. Clark *et al.* (1956) have recently described the successful removal of a lung containing multiple congenital cysts. Successful removal of congenital lung cysts has also been described by Fischer *et al.* and by Conway. There appears little doubt that the congenital cysts in Case 12 were primarily responsible for the fatal lobar emphysema from which the patient suffered, and an attempt at operative removal should have been made.

Post-pneumonic pneumatocoeles, which constitute the main differential diagnosis from congenital cysts usually have a good prognosis and tend to disappear spontaneously. Where, as is so frequently the case, congenital cysts or acquired post-pneumonic cysts are subject to tension emphysema the valvular mechanism seems usually to be that which occurred in Case 10. The tangential opening of the supplying bronchus into the cyst results in a slit-like or flap-like mouth which acts as a valve and whose valvular nature tends to be preserved by the pressure in the cyst (Fig. 1). There is thus a vicious cycle of events maintaining the obstructive emphysema within the cyst. Some factor suddenly breaking this cycle may be responsible for the sudden disappearance of, for example, a post-pneumonic pneumatocoele. Clark *et al.* (1956) have suggested that multiple congenital cysts of the lung can result from the presence of both bronchiolectasis and a check-valve obstruction of the bronchus. In the presence of the increased tension within the lung resulting from the check valve the bronchiolectatic areas distal to the valve expand to form cysts.

Mixed Forms of Regional Obstructive Emphysema

Although it is convenient and possibly useful to classify obstructive emphysema into three main types these may not occur in a 'pure' form. Case 12 illustrates a 'mixed' form in which cystic and lobar emphysema were combined. The assertion of Clark *et al.* (1956) that areas of congenital bronchiolectasis may become cystic in the presence of a check-valve obstruction of a main bronchus causing lobar emphysema suggests another mixed form.

Summary

It is suggested that regional obstructive emphysema can be classified as lobar, lobular or cystic with subsidiary groupings dependent on pathogenesis.

A series of cases in infants is reported illustrating varieties of regional obstructive emphysema. These are classified according to the scheme outlined above.

Diagnosis is discussed and the important role of obstructive emphysema in the production of respiratory symptoms in infancy is emphasized.

The mechanism of production of the various forms of regional obstructive emphysema and their treatment is considered.

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AN INBORN ERROR OF METABOLISM WITH THE URINARY EXCRETION OF α-HYDROXY-BUTYRIC ACID AND PHENYLPYRUVIC ACID

BY

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We have recently seen a baby girl with gross mental deficiency who had repeated attacks of generalized oedema. She also had an extremely unpleasant, pungent smell due to the presence in her urine of a substance derived from α-hydroxy-butyric acid. So far as we know, this acid has not previously been detected in human urine. The urine also contained phenylpyruvic acid and phenylacetic acid as well as an excess of certain amino-acids.

We believe that the infant had a double metabolic abnormality. One was the familiar defect of phenylketonuria in which a block in the conversion of phenylalanine to tyrosine leads to the accumulation of phenylalanine in the body and to the excretion in the urine of phenylpyruvic acid, phenylacetic acid and other derivatives of phenylalanine (Jervis, 1954). The urinary excretion of α-hydroxybutyric acid cannot be related to the metabolism of phenylalanine and indicates the presence of another metabolic defect.

Clinical History

Mary D. was the first baby of healthy, unrelated parents, and was born normally in a maternity hospital. She breathed and cried at birth but from the beginning she refused the breast. From the first day of life she had an unusual and unpleasant smell. On the fourth day she developed occasional extensor spasms and was extremely pale, listless and unresponsive to stimuli. She was at that time thought to have a severe cerebral abnormality.

On the ninth day of life she first came under our observation. She was quite flaccid and unresponsive to stimuli. The fontanelle tension was increased and the head circumference was 14 inches. She lay motionless and required tube feeding. The curious smell which had been noticed on the first day of life was still present. It hung about her room and clung to her clothes and the clothes of those who nursed her. It was described by different observers as smelling 'like an oast house', 'like burnt sugar' and 'like dried celery'. The source of the smell was her urine.

Further investigations at this time gave the following results:

Lumbar Puncture. Normal pressure, clear fluid, no cells and protein 120 mg./100 ml.

Subdural Puncture. There was no evidence of subdural collections.

Serum. The urea level was 41 mg./100 ml., potassium 3·1 mEq./l, calcium 5·1 mEq./l and total protein 7·8 g./100 ml.

During the first six weeks of life she improved sufficiently to feed from a bottle and was able to go home. She remained hypotonic and completely unresponsive to stimuli, never taking notice of anything or attempting to raise her head. She had long spells of loud, monotonous crying little affected by sedation.

Between the ages of 5 and 10 months she had frequent episodes of fever, rapid breathing and generalized pitting oedema. There was no evidence of congestive heart failure. The first attack was regarded as due to infection and treated with chemotherapy. Subsequently, however, she often recovered within a matter of 12 to 24 hours from attacks for which no chemotherapy was given.

At 9 months she had grown a small amount of completely white hair. She had also increased in size (weight 20 lb. and head circumference 17 inches) but remained mentally defective and responsive only to painful stimuli. The characteristic smell persisted in the urine throughout life. At 10 months she died at home.

Necropsy Report

Dr. J. Hart-Mercer reported as follows:

The body weighed 7·75 kg. (within normal limits). It was 'well nourished', *i.e.*, the subcutaneous fat was abundant, measuring up to 1·5 cm. on the anterior abdominal wall. The head circumference was 42 cm. (a little small for the age). The scalp hair was very blonde and fine.

The internal appearance showed evidence of terminal inhalation of bilious vomit into the bronchi.

The thymus (12 g.) showed some degree of accidental involution.

There were a few fibrous pleural adhesions in the left interlobar fissure, and marginal emphysema and moderate emphysema bilaterally. Foci of broncho-pneumonia were found in both lungs, particularly in the lower lobes, associated microscopically with pneumococci.

All the chambers of the heart were slightly dilated.

The liver was slightly enlarged (to 284 g.) and microscopically merely showed venous congestion with centrilobular degenerative and atrophic changes in the liver cells.

The spleen weighed 17 g. and was a little smaller than normal. It showed *fleckmilz*, *i.e.*, multiple small foci of recent and developing necrosis affecting irregular areas of pulp and lymphoid tissue. Resembling early infarcts, they were not apparently associated with gross arterial change but recent thrombi were encountered in occasional arterioles.

The kidneys weighed together 133 g., about twice the normal combined weight. The enlargement was bilateral and diffuse, the subcapsular surfaces smooth, the cortices pale. Microscopy showed hypertrophic-looking proximal convoluted tubules lined by unusually tall epithelium. In many of these cells there was hyaline droplet degeneration.

The glomeruli were largely unaltered, but here and there thrombus or thrombus-like eosinophilic material occluded one or more capillary loops.

The cells of the lower nephrons frequently showed lipid droplets in their cytoplasm and occasionally their lumen was distended with hyaline cast material.

The brain weighed 700 g., a little small for the age. Neither externally nor on section was there evidence of gross maldevelopment. Indeed the appearances were almost normal. The width of the white matter in the cerebral hemispheres may have been slightly reduced but the only convincing change was the unduly soft consistency of all parts of the brain.

Microscopic examination showed widespread changes in cerebrum, brain-stem and cord suggesting a nutritional encephalomyelopathy with widespread defect of myelinization.

Examination of Urine

The urine during life was a clear, amber-coloured liquid with the characteristic penetrating smell already described and which did not diminish during storage at 4° C. The reaction was acid to litmus, no albumin was present and no formed elements were found on repeated microscopy.

The first specimen gave a slight reduction with Benedict's qualitative reagent on one occasion which was shown to be due to glucuronic acid.

Phenylketonuria. The addition of a few drops of ferric chloride to the urine gave a fairly persistent emerald green colour which was consistent with the presence of phenylpyruvic acid. The colour was more intense if the urine was acidified, extracted with ether and a drop of ferric chloride added to the extract. The characteristic smell was found to be extracted at the same time; since this did not happen when alkaline urine was similarly extracted it could be concluded that the pungent-smelling substance was acid in nature. The phenylpyruvic acid was quantitatively estimated by a slight modification of the method of Berry and Woolf (1952). A freshly synthesized and purified sample of phenylpyruvic acid (Herbst and Shemin, 1939) was used for the calibration curve. The concentration was found to be 8·96 mg./20 ml. urine or 134·4 mg./24 hours.

Phenylpyruvic acid is an oxo-acid and as further confirmation of its presence it was decided to make 2·4 dinitrophenylhydrazine derivatives of all the oxo-acids in the urine by the method of Cavallini, Frontali and Toschi (1949). The extract of the derivatives from the urine was compared chromatographically with derivatives prepared from a series of oxo-acids. The 2·4 dinitrophenylhydrazine derivative of phenylpyruvic acid was prepared from the freshly synthesized acid by the method of Smith and Jones (1948). The solvent phase of tert-amyl alcohol, 50 parts; ethyl alcohol, 10 parts; water, 40 parts, was used as the developing solvent (Altmann, Crook and Datta, 1951) on Whatman No. 3 paper buffered to *p*H 6·0 or *p*H 7·0. An additional reason for examining these oxo-acid derivatives was the fact that the acids in dilute solution in water have smells somewhat similar to that of the urine.

The keto-acids chosen were α-oxo-butyric, oxo-glutonic, pyruvic, α-oxo-glutaric, acetoacetic, p-hydroxy-phenylpyruvic, oxo-malonic and laevulinic. The spots needed no development since the derivatives were yellow. The phenylpyruvic acid derivatives had an R_F of 0·66 on paper buffered to *p*H 6·0 and 0·60 on paper buffered to *p*H 7·0.

The urine showed only one derivative which had the same R_F as the phenylpyruvic acid on paper at both *p*H 6·0 and *p*H 7·0. This was a useful confirmatory test for phenylpyruvic acid. Nearer the solvent there was a discrete unstained area of the paper which contained a substance with the characteristic smell of the patient's urine. The smell was therefore not due to an oxo-acid. It was easy to demarcate the area by smell and so assign an R_F value of about 0·8 to the unknown colourless substance.

The Identification of the Unknown Substance. In order to identify this strongly smelling non-ketonic, ether-soluble substance, a 25 ml. sample of urine was acidified to *p*H 1·0 with concentrated HCl and extracted three times with 25 ml. ether. The combined extracts were evaporated by a stream of nitrogen and the residue dissolved in a small volume of ether. This extract was compared against a series of aliphatic and phenyl-substituted aliphatic acids by paper chromatography. The developing solvent used was propanol, 60 parts; ammonia, 30 parts and water, 10 parts (Buffs, Peters and Wakelin, 1951). Whatman No. 3 paper was used unbuffered and found to give more discrete spots than the thinner papers. The acids used for comparison were phenylpyruvic acid (freshly prepared), phenylacetic acid, β-hydroxy-butyric acid and α-hydroxy-butyric acid. These derivatives of butyric acid were used because their smell in dilute aqueous solution was very similar to that of the urine. The chromatogram was run overnight

(about 12 hours) dried in air and the spots developed by spraying the chromatogram with 'universal indicator' (B.D.H. Ltd.) adjusted to a purple colour with sodium hydroxide (Long, Quayle and Stedman, 1951). A more even spray was obtained when alcoholic potassium hydroxide was used to adjust the colour. The ammonium salts of the acids showed up as red spots on an originally purple background which quickly faded. The urine extract was found to give three acid spots of R_F values 0·56, 0·62 and 0·76. The slowest running spot was equivalent to that of phenylpyruvic acid and the others were equivalent to α-hydroxy-butyric acid which itself gave rise to two spots. The fastest moving spots of both the urine and the pure α-hydroxy-butyric acid (R_F 0·76) possessed the characteristic smell originally noticed in the urine. Pure phenylacetic acid had an R_F of 0·75 and hence was not separable from the α-hydroxy-butyric acid.

As a confirmation of the identity of the smell with α-hydroxy-butyric acid, a sample of the urine extract was allowed to stand at room temperature for a few days during which time the phenylpyruvic acid decomposed. This could be shown by a negative ferric chloride test and chromatographically, but the smell remained just as persistent. This old extract was also run in a different solvent system of butanol, 95 parts; formic acid, 5 parts; saturated with water (Lugg and Overell, 1948). The completed chromatogram was sprayed with 'universal indicator' but dried in air for a longer period than previously. Both the urine and the α-hydroxy-butyric acid gave two spots each of R_F 0·77 and 0·85 but now in each case the smell was associated with the slower moving component.

The method of formation of the smell was investigated by producing further chromatograms of α-hydroxy-butyric acid in propanol ammonia in an atmosphere of cyanide (by placing in aqueous solution of potassium cyanide in a tank) to inhibit oxidation. The area of the fastest moving spot was relatively much smaller than previously. This suggested that the smell was due to an oxidation product of α-hydroxy-butyric acid which had previously been increased in amount during chromatography.

Phenylacetic Acid. In the previous chromatograms one of the spots of α-hydroxy-butyric acid had a very similar R_F value to phenylacetic acid. Although we suspected the presence of the latter substance, proof had not been obtained. This was done by using a different solvent. This solvent was benzene, 40 parts; formic acid, 40 parts; and water, 20 parts (Bray, Thorpe and White, 1950). With it the old urine extract gave spots of R_F 0·23, 0·55, 0·77 and 0·88. The three slower moving spots were the same as those given by α-hydroxy-butyric acid and the fastest moving one was the same as that given by phenylacetic acid. The characteristic smell of the urine was associated with the spots with R_F values of 0·55 and 0·77 and the different smell of phenylacetic acid was associated with the spot of R_F 0·88.

Amino-acids. Routine two-dimensional ascending paper chromatography in phenol-water-ammonia and collidine-lutidine-water (Dent, 1948) was performed on the urine. This showed an excess of phenylalanine, methionine and tyrosine. A further modification consisted of evaporating the urine to dryness under reduced pressure and extracting the amino-acids with acetone. The acetone extract was compared with the other amino-acids by one-dimensional descending paper chromatography with the solvent propanol, 60 parts; ammonia, 30 parts; water, 10 parts. On dipping the dried chromatogram in 0·1% ninhydrin in acetone and drying for five minutes at 100° C., large amounts of phenylalanine, methionine and tyrosine were demonstrated. There was, however, no evidence of α-amino-butyric acid which had been suspected as the source of the α-hydroxy-butyric acid.

All these results were confirmed in post-mortem urine.

Discussion

The child presented a clinical picture similar in some respects to that of phenylpyruvic oligophrenia. Unusual features were marked unresponsiveness to stimuli, muscular flaccidity, recurrent episodes of pyrexia with generalized oedema and a penetrating smell in freshly passed urine. This smell bore no resemblance to that of phenylacetic acid which is commonly associated with phenylketonuria. It effectively masked the smell of that substance which was also in the urine.

The urinary findings established that the baby had a metabolic defect producing phenylketonuria together with another abnormality leading to the excretion of α-hydroxy-butyric acid in the urine. The odour was so characteristic that it should be easy to recognize any further examples of this condition. The smell was probably due to an oxidation or polymerization product of α-hydroxy-butyric acid, since it was reduced in amount on paper chromatography in an atmosphere of cyanide. It was associated with a single spot except in chromatography performed in benzene, 40 parts; formic acid, 40 parts; water, 20 parts, in which two spots with the characteristic smell were found. The α-hydroxy acids tend to polymerize together and to form lactones as shown in Fig. 1 for α-hydroxy-

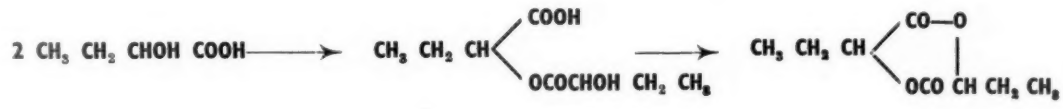

FIG. 1.

butyric acid. This should account for the multiple spots in chromatograms of this substance.

Abnormal excretion products other than phenylpyruvic acid have been detected in the urine of patients with phenylketonuria and are listed by Jervis (1954). These are phenyllactic, p-hydroxy-phenyllactic, phenylacetic, p-hydroxy-phenylacetic and o-hydroxy-phenylacetic acids. The chemical relationships between those substances are shown in Fig. 2 and it is probable that all can be derived from phenylalanine. Of these only phenylacetic acid was detected in the urine of the patient we are discussing. Normally the acids with a hydroxylated benzene ring are derived from tyrosine, but in phenylketonuria it is possible they are derived from hydroxylation of the derivatives of phenylalanine.

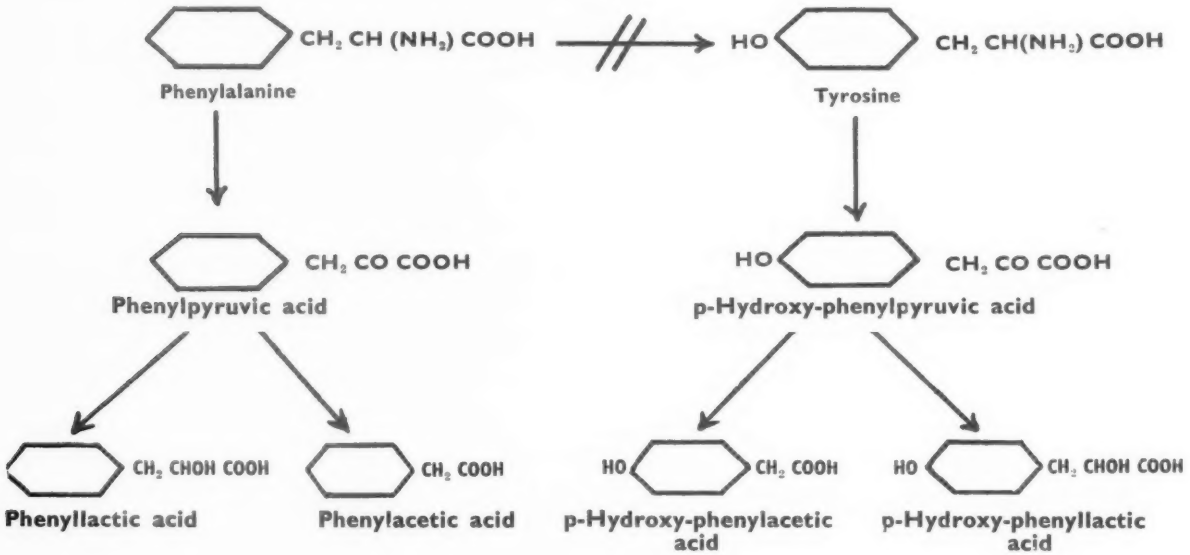

FIG. 2.

The presence of α-hydroxy-butyric acid cannot be explained from this system and its origin in intermediary metabolism must at present remain uncertain. It is unlikely to be formed in the oxidation of fat since this leads to the formation of oxo- and hydroxy derivatives in the β position. A possible source is from α-amino-butyric acid and thence by reduction perhaps by bacteria to the α-hydroxy compound as shown in Fig. 3. This type of hydrolytic deamination is known to take place in bacteria (Baldwin, 1947) and it is possible that bacteria in the renal tract were responsible for it in our patient. No urinary infection, however, was detected and the smell was present in freshly passed specimens, and within a few hours of birth. The amino-acid analogue of α-hydroxy-butyric acid, α-amino-butyric acid, has been shown in human urine (Dent, 1947) but it was not detectable in our patient.

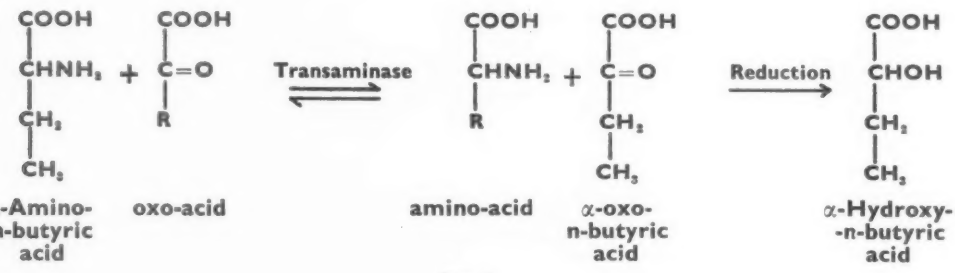

FIG. 3.

α-Oxo-butyric acid may be linked to the meta-

bolism of many other amino-acids as shown by experimentation in mutated bacteria. Carroll, Stacey and du Vigneaud (1949) have shown that α-oxo-butyric acid occurs in the catabolism of homoserine and Lien and Greenberg (1953) have shown that the same compound occurs in the metabolism of threonine. It has also been shown by Umbarger and Adelberg (1951) that α-oxo-butyric acid can be used in the synthesis of isoleucine and valine from simpler substances. So far there has been no evidence of similar mechanisms in humans.

The absence of any signs during life or at necropsy of renal infection and the fact that the distinctive smell was present in fresh specimens of urine incline us against the view that the α-hydroxy-butyric acid was produced wholly or in part by bacterial action. We regard it as more probable that its presence was due to a defect in intermediary metabolism and that this was a major factor in causing the child's illness.

Summary

A child is described in whom a syndrome of mental deficiency and recurrent episodes of oedema were associated with the urinary excretion of α-hydroxy-butyric acid and phenylpyruvic acid.

The presence of α-hydroxy-butyric acid gave rise to an unusual smell.

Phenylacetic acid, phenylalanine, tyrosine and methionine were also present in excess in the urine.

Some possible modes of formation of the α-hydroxy-butyric acid are discussed.

We wish to thank Dr. A. L. Latner for his advice and criticism throughout the course of the investigation, and also Prof. S. D. M. Court and Dr. F. J. W. Miller for help in the preparation of this paper. We are grateful to Dr. J. Hart-Mercer for the necropsy report.

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A CASE OF HARTNUP DISEASE

BY

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This new disease was first described last year by Dr. Hart and Professor Dent and their colleagues (Baron, Dent, Harris, Hart and Jepson, 1956) under the title 'Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant amino-aciduria, and other bizarre biochemical features'.

The name 'Hartnup disease'—after the family then described—was later used in a reference to the syndrome by Harris (1957) and is that at present preferred by the original authors. No further accounts of cases have yet been published in this country and it seemed, therefore, that the following case was worthy of record. A brief reference to two further cases in Holland has been made by Jonxis (1957).

Angela P. was born on July 1, 1947, the second child of healthy, unrelated parents. Her infancy and early childhood were uneventful; she had most of the childhood infectious fevers but otherwise was well and grew normally. In March of 1952 she developed diarrhoea which was treated with a sulphonamide but did not clear up for nearly three weeks.

She was first seen in consultation on May 13, 1952, at the age of 4 years 10 months, on account of recurring attacks of unsteadiness, in some of which she fell and hurt herself. These episodes started shortly after the diarrhoea had cleared up. At about the same time she began to develop a rash on the face and lower parts of the arms. This rash was always made worse by exposure to the sun; it had been diagnosed as sensitivity to sunlight and was being treated with only partial success by protective creams. Her appetite was poor and she was rather temperamental. Apart from a mild ataxia there was little to be found abnormal in the nervous system.

When seen again six weeks later it was clear that there had been some deterioration: she was now unsteady at all times when on her feet, sometimes she felt giddy when walking about and would then sit down if possible; at other times she fell—rather more often to the left than to the right. The rash was as bad as ever and caused her a good deal of inconvenience. These troubles were making her more temperamental and difficult at home. She was admitted to hospital for five days on July 2 1952.

The clinical examination showed a girl of average physique, definitely ataxic whenever she walked. When walking about the ward she would sometimes appear to feel giddy or unsteady and would quickly sit down, but it was clear that she was constantly ataxic. The legs showed no wasting and the tendon reflexes were all slightly exaggerated. The plantar reflexes were flexor. The arms showed definite but mild intention tremor with increased tendon reflexes, but she could feed herself, play with toys and fasten buttons. No sensory disturbance could be made out. There was no papilloedema and no affection of any of the cranial nerves. A radiograph of the skull was normal. The urine showed no abnormalities.

The rash was quite striking, being only on the exposed areas of the body, and was very marked on the back of the neck, most of the face, the backs of the hands and outer surfaces of the arms—strictly to the sleeve level—and the dorsal surface of the feet where exposed through the straps of the sandals, the calves and knees to the lower limit of the dress. The skin in the affected areas was reddened, rough and dry; in a few areas it was thickened. Round the mouth and external nares there was hardening and cracking at the muco-cutaneous junctions.

The child was fretful during her stay, unhappy and anxious to get home. She did not vomit, her appetite was indifferent and she had no headache. No definite diagnosis was reached and she was allowed home.

When she was followed up six weeks later in the middle of August, it was reported that her unsteadiness was much more marked; she could only walk for a few yards and now moved about very little, being especially diffident about going up or downstairs.

Examination showed a more marked ataxia with very unsteady gait; she walked with a rather wide base and could only manage a few steps without support. The deep reflexes were still exaggerated. The arm and hand movements were jerky, there was intention tremor and she could feed herself only with considerable difficulty. The ocular fundi were normal. There was mild nystagmus, not very well sustained, detectable in both lateral directions. Her speech was rather slow and at times she tended to split up words. The rash was slightly more marked. She also had an angular stomatitis, a very slight atrophic glossitis, and a mild vulvitis. The hair was soft and loose, coming out readily when brushed and combed.

In view of the increasing severity of her symptoms she was transferred to The Hospital for Sick Children, Great

Ormond Street, on August 27, 1952, under the care of Dr. P. R. Evans.

Investigation there confirmed the above findings, and the photographs (Fig. 1) show clearly the distribution of the rash. The cerebrospinal fluid was clear and contained no cells; protein was 30 mg. per 100 ml.; sugar, 91 mg./100 ml.; chlorides, 700 mg./100 ml.; and W.R. negative. The urine showed no porphyrins, but there was an increase in the amino-acid content.

Dr. Evans noted that the dermatitis in its appearance and distribution closely resembled that seen in pellagra and suggested that the other symptoms might also be due to vitamin B deficiency.

Treatment was therefore started on September 2 with riboflavin, 3 mg. t.d.s., and nicotinamide, 10 mg. four times daily, by mouth. She was given a high-protein diet, with added brewers' yeast. The skin was treated with cremor calamine.

Within a week of starting specific treatment it could be seen that the ataxia was less marked and the skin lesion definitely improving. After two weeks, improvement had reached the stage where she could walk without support. The deep reflexes were still brisk. She could now feed herself much more readily. After four weeks, a test dose of ultra-violet light still showed some skin sensitivity.

After eight weeks' treatment she had gained 4 lb. in weight. She had apparently quite recovered and was allowed home on October 25, 1952, with instructions to take riboflavine and nicotinamide for a further three months.

A few months later she was reported to be perfectly well, attending school regularly and showing no behaviour difficulties.

Further retrospective enquiry into possible causes of the 'pellagra' syndrome suggested that her diet might have been partly to blame, as she had, for some months before her symptoms developed, lived largely on cornflakes and milk. There seemed to have been an association in time between the attack of diarrhoea and the first appearance of rash and ataxia, and it was felt that this illness and its treatment with sulphonamide over a period of two to three weeks might have interfered with the absorption of vitamins.

The publication by Baron, Dent, Harris, Hart and Jepson (1956) of details of the Hartnup family, and their consideration of two other children described in the British literature as having 'pellagra' seemed to provide an answer to this unresolved diagnostic puzzle. Angela was seen again and a specimen of urine was analysed by Professor C. E. Dent who reported that 'the chromatogram shows a gross disorder of amino-acid excretion, identical with that of our other cases of Hartnup disease'

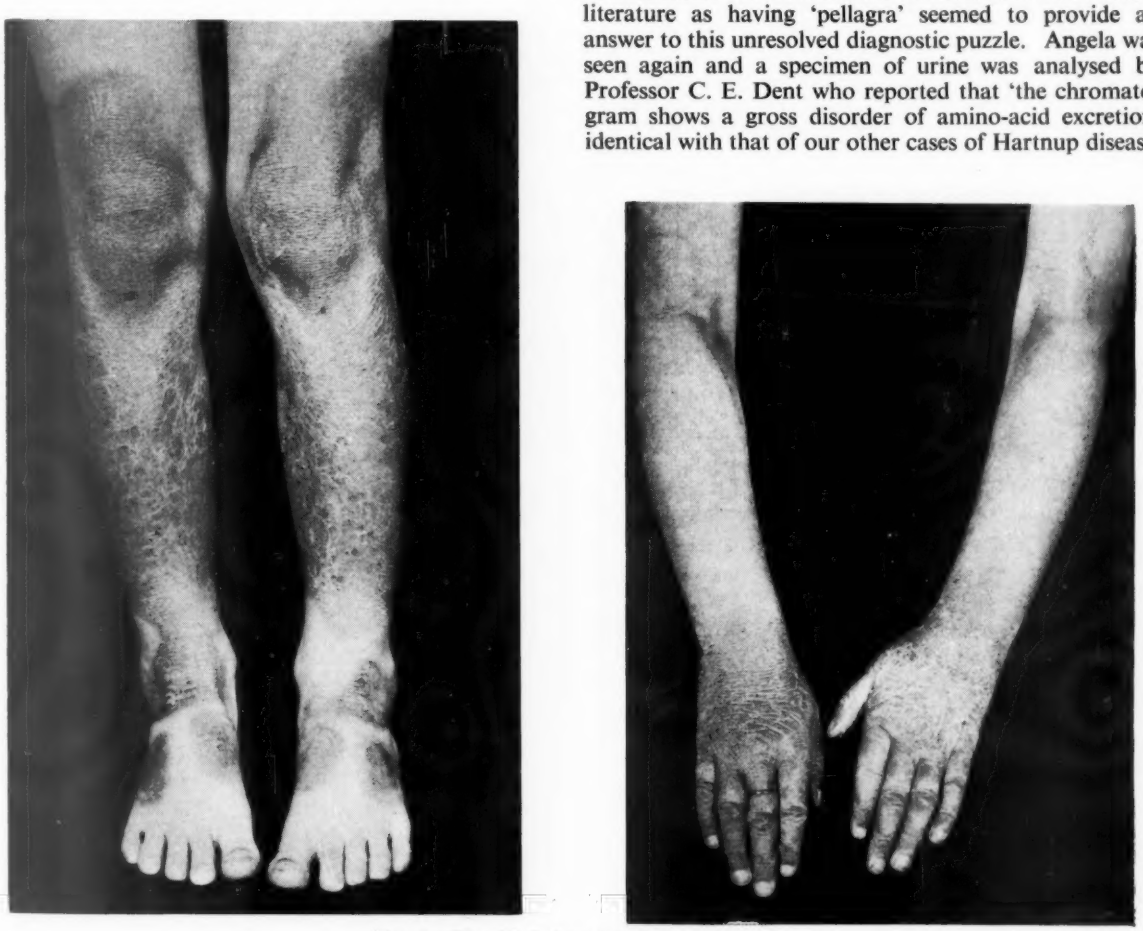

FIG. 1.—The skin lesions (September 1, 1952).

(Fig. 2). 'Indole chromatograms were also carried out (by Dr. Jepson) and showed the usual gross excretion of tryptophan, indican, indolylacetic acid and indolylacetylglutamine in the pattern characteristic of the disease.'

A detailed investigation of the genetic background in this case has been undertaken and a family tree constructed (Fig. 3).

Angela's father died suddenly in 1955 at the age of 44 from a coronary thrombosis. The paternal grandfather

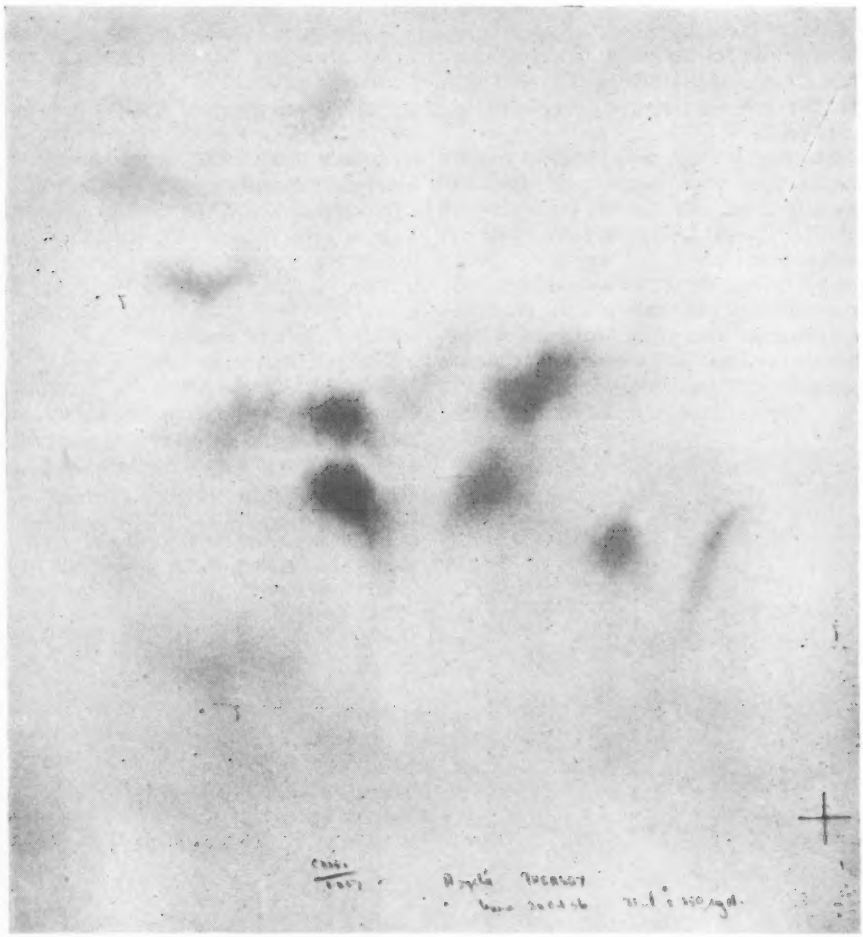

FIG. 2.—Urinary amino-acid chromatogram showing the typical pattern of amino-acid excretion.

At this time, it was noted that she was fit and well, and normally grown for her age. Her I.Q. has not been tested but she shows no evidence of slow mental development. In the intervening three years she had shown no further ataxia and clinical examination of the central nervous system showed no abnormal signs. Her skin, however, continued to show mild sensitivity to sunlight: the backs of the neck and hands readily became reddened and thereafter soon became sore if not treated with calamine lotion. In summer she has to be careful not to expose herself too much in the sun. She has been given no more nicotinamide.

died at about 70, and the paternal grandmother at 78. The cause of death is not recorded in either case. The maternal grandfather died at 74 of a coronary thrombosis, and the maternal grandmother at 63 of asthma and bronchitis. One of Mrs. P.'s sisters died at the age of 4 years, and a niece died at the age of 9 months, but in neither case is the cause of death recorded.

The urines of 26 of the 31 living relatives (including aunts and uncles and their offspring) have been tested by Dr. H. Harris for amino-acids but none shows the characteristic chromatogram of Hartnup disease.

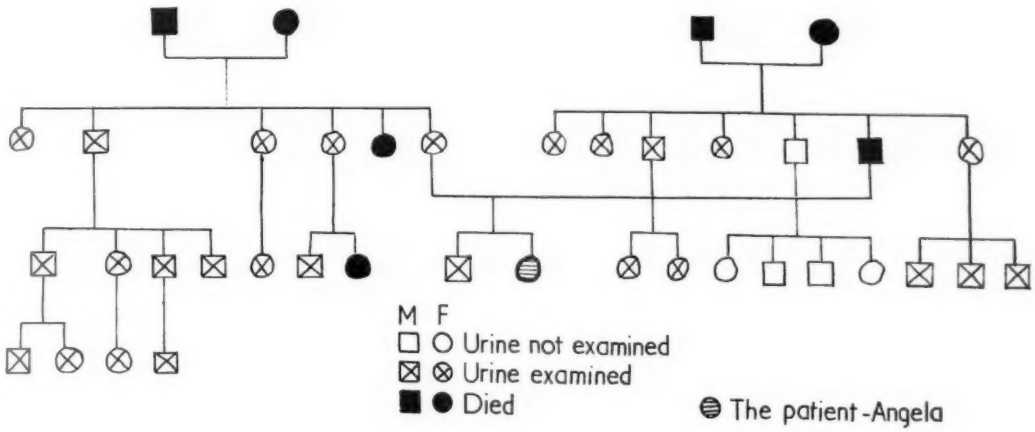

FIG. 3.—The family tree.

Summary

A case of 'pellagra' in an English child of 4½ years is described. There was a very satisfactory clinical response to large oral doses of riboflavine and nicotinamide and recovery appeared to be almost complete.

Subsequent investigation at the age of 9½ years has shown the cause to be the characteristic renal amino-aciduria and other biochemical disturbances associated with Hartnup disease.

I am very grateful to Dr. P. R. Evans for his help in the early stages of this case and to the Department of Medical Illustration, The Hospital for Sick Children, Great Ormond Street, for the clinical photographs; to Professor Dent for his help and encouragement and for permission to reproduce the chromatogram; and to Dr. H. Harris for the family tree.

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DISSOCIATION AS A GUIDE TO DEVELOPMENTAL ASSESSMENT

BY

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In the assessment of an infant's development, in the light of the mother's developmental history and of one's own developmental examination, one considers not only how far one's findings tally with the mother's history, but the relationship of one field of development to another. For instance, if a child's speech development is quite out of step with his motor development, an attempt to determine the reason for it and its significance must be made. Such a departure from the usual relationship of one field of development to another may be termed 'dissociation'. It is a common and important finding which has received little or no attention in the literature. For convenience I shall consider it in different fields of development.

Delayed Motor Development Without Retardation in Other Fields

The commonest cause of delayed motor development in an infant is mental deficiency; but in mental deficiency there will also be retardation in other fields of development such as social behaviour, interest in surroundings, and speech, for no child with isolated delay in motor development can be mentally defective.

Obvious causes of isolated motor retardation are hypotonia and hypertonia. Rare causes include infantile myopathies, diastematomyelia and other purely mechanical defects.

Hypotonia. The causes of hypotonia have been reviewed by Walton (1956, 1957) and need not be recapitulated here. They include amyotonia congenita and allied conditions. Hypotonia sufficient to cause significant motor retardation could hardly be missed. In the developmental history and examination there is a striking dissociation between the grossly retarded motor development and the normal social behaviour. For instance, the child has begun to smile at the usual age (4 to 6 weeks), to vocalize his pleasure two or three weeks later, to take a normal interest in his surroundings, to follow his mother's movements with his eyes (at 2 or 3 months of age), and to turn his head to sound at about 3 months. Later on he has shown excitement at feed times, and has imitated his parents in sounds and simple movements (6 to 9 months). His vocalizations have followed the usual pattern and his speech has developed at the usual time, so that he says three or four words with meaning by 12 months, and has joined two or three words together by 21 to 24 months. On the other hand, he is grossly retarded in head control, and subsequently in sitting, creeping and walking. An illustrative case history is as follows:

When this girl was seen at 13 months her head control was that of a 10-weeks-old baby. The manipulative development was average. She was saying single words with meaning. There was generalized hypotonia, and as the knee jerks were present the diagnosis of congenital hypotonia was made. Subsequently she put words together at 27 months and walked without help at 5 years.

This child has a mild congenital hypotonia with an average intelligence. The normal social and subsequently normal speech behaviour would preclude the suspicion of mental deficiency.

Less easy to assess is the combination of mental deficiency with hypotonia. This is not a particularly common combination, but the complication of hypotonia might well lead to too gloomy a prognosis for intellectual development because of the severe motor retardation. One should look for a glimmer of hope in the relationship of the motor defect to other fields of development. In uncomplicated mental deficiency there tends to be relatively less retardation in motor development than in social behaviour and speech. When there is an additional mechanical difficulty, such as cerebral palsy, that position is reversed. One might find, therefore, that there is very severe motor retardation with only moderate retardation in speech. This would indicate a motor defect with an only moderately low intelli-

gence quotient (I.Q.). The case of cerebral palsy described below is an example.

Acrodynia (pink disease) may present a confusing picture, in that the mother's history indicates that early development was normal, and that deterioration in motor development then ensued.

An 8-month-old child was referred for confirmation of the diagnosis of mental defectiveness. The mother was not able to give a reliable developmental history. The child's head control (when placed in the prone and when pulled to the sitting position) was that of a 4-month-old baby, but he was interested in test objects. His manipulative development was not less than that of an average 8-month-old baby. His grasp of a 1-in. cube was a mature one, with a rapid transfer to the other hand. He was seen to chew. He was markedly hypotonic and other signs of acrodynia were found. He made an uninterrupted recovery and became a normal child.

The dissociation between the delayed motor and normal manipulative and social behaviour showed immediately that this boy could not be mentally defective, but that there should be a mechanical difficulty affecting his gross motor development.

Rickets, which is now hardly ever seen in this country, would give a similar developmental picture, because of the hypotonia with which it is associated.

Severe illness may cause delay in motor development because of the poor muscle tone which it induces while development in other fields is likely to be normal.

Hypertonia. Cerebral palsy presents considerable developmental problems because it is seen in several different forms; there are all degrees of severity, and it is so frequently associated with a low level of intelligence which itself greatly affects the child's development.

The diagnosis of spastic paraplegia can often be made in the older infant on the history alone, provided that the intelligence is average. There is a story of normal social development (smiling by the age of 6 weeks, and so on), with normal manipulative development (voluntary grasping by 5 months), normal speech, but grossly delayed walking. The age of sitting may or may not be normal. The mother may have noticed stiffness of the lower limbs. The diagnosis is confirmed by the physical examination. The following history is an example:

A girl grasped objects voluntarily at 5 months, sat unsupported at 8 months, was helping her mother to dress her at 13 months (by holding her arm out for clothes and the foot out for a shoe) and spoke in sentences at 23 months. She was not able to walk at 5 years. She had a paraplegia with a normal I.Q. (The school medical officer assessed her on the Terman-Merrill scale as 'average' at 5 years without giving a figure.)

A mild degree of paraplegia can easily be missed in the early months.

I observed a child from 10 months of age on account of defective head control. There was no retardation in other fields. I suspected paraplegia, but subsequently decided that the knee jerks were within normal limits. There was no adductor spasm on abducting the hips. I saw the boy repeatedly, and eventually when he was 4 years old found undoubted evidence of mild disease of the pyramidal tracts involving the lower limbs. There was no deformity. He had learned to sit without support at 14 months, to feed himself with a cup at 18 months, and to join words together at 23 months. He was not able to walk at 4 years. At that time his developmental age in fields other than walking was 40 months.

Unfortunately, an average level of intelligence is unusual in cerebral palsy, so that one has the confusing picture of two factors combining to affect and retard development. Here the phenomenon of dissociation is of real value in developmental prognosis. It is particularly important to assess the child's interest in surroundings, his powers of concentration and speech. Whereas a mentally defective spastic child will make little effort to grasp an object, a spastic child of the same age and degree of spasticity but with a good level of intelligence will make determined efforts to grasp. Hence one notes the dissociation between the physical disability and the powers of concentration. If retardation in speech is only slight, severe mental deficiency is impossible: hence it is a most important indication to look for in assessing a child with cerebral palsy. Naturally speech is often retarded by other factors, such as deafness, in the presence of a good level of intelligence, so that no absolute reliance can be placed on the absence of speech as an indication of low intelligence.

A 24-month-old child was referred with a diagnosis of mental deficiency. He began to grasp objects voluntarily at 10 months, but was not able to sit. He began to say words with meaning at 18 months and to join words together at 30 months.

This gross motor delay with only a moderate delay in speech would suggest a severe mechanical disability with only a moderately low I.Q. He had a spastic quadriplegia, and his I.Q. at 5 years was 71.

A possibility to consider on finding isolated motor retardation is the subsequent development of athetoid movements, indicating that the child is in fact suffering from athetosis. It is by no means always the case, however, that motor retardation is found in early infancy in children who will subsequently be shown to be athetoids, for, provided that the I.Q. is average, the motor development in

some of these children is normal. One would certainly bear the possibility in mind if there were a history of severe perinatal anoxia, of improperly treated haemolytic disease of the newborn or hyperbilirubinaemia with prematurity.

Other Causes. There remain some cases of isolated motor retardation in which even prolonged observation fails to reveal any sign of organic disease.

A baby, aged 7 months, was referred by a paediatrician because of defective head control. He had been examined with regard to suitability for adoption. On examination his head control (when prone and when pulled to the sitting position) was that of a 3-month-old baby, but his manipulative development was that of a 7-8 month baby. His interest in surroundings and his alertness seemed average. He was able to chew. There were no signs of cerebral palsy. I expressed the opinion that this was merely isolated motor retardation. His subsequent history showed that he spoke single words and sat without support at 1 year, put words together at 18 months and walked without help at 23 months. Subsequent examination showed that he was normal in all respects, with an I.Q. of just over 100.

In view of his prospective adoption, the responsibility of making a correct diagnosis was a big one.

Normal Motor Development with Retardation in Other Fields

One occasionally sees a child in whom motor development is within 'normal' limits but in whom defective social and speech development leads to a diagnosis of mental deficiency. It is not rare to see relatively advanced motor development in mongols in early infancy—a fact noted by Gesell.

I observed a mongol who began to smile at 4 months, to grasp objects voluntarily at 6 months, and to sit unsupported at 7½ months. At this time his interest in his surroundings was very defective. Development then slowed down, and he only began to walk without help at 34 months and to put words together at 69 months. At this age his I.Q. was 28. I saw another mongol who at 8 months was sitting securely without support, quite as well as an average baby; but his interest and concentration were notably defective, and he showed hand regard—normally lost by 16 weeks. His I.Q. subsequently was 30.

A girl sat without support at 7½ months, and walked without help at 21 months. Concentration was poor. She was only able to say six words at 39 months. At five years her I.Q. was 50. Another girl sat without support at 8 months, and walked without help at 17 months, but there was no speech and concentration was poor. There was full sphincter control by 24 months. She began to say single words at 3 years and to put words together at 5. At ten years her I.Q. was 20. Another girl sat without support at 6 months, and walked without help at 18 months, but I was impressed by the aimless hyperkinesis, defective concentration, and delayed speech development. Her I.Q. at 56 months was 52. In none of these cases was there any degenerative disease of the nervous system or deterioration in performance.

Other Variations in Motor Development

One sometimes sees the picture of a 'slow-starter'—a child who is seriously retarded in motor development in the first few weeks and then catches up.

A child with a birth weight of 5,000 g. and a normal perinatal history had a complete head lag at 13 weeks like that of a newborn baby and did not follow with the eyes till 17 weeks or smile till 18 weeks. From that time she made rapid strides in development, and at 25 weeks her head control was that of a 16-week-old baby. She sat without support at 7½ months, and walked without support at 1 year. She was able to say ten words with meaning at that age. Her I.Q. at 5 years was 122.

Some children develop normally for the first few weeks and then develop thyroid deficiency, encephalitis, or signs of a degenerative disease of the nervous system. When these develop suddenly, as in the development of akinetic seizures with hypsarrhythmia (Illingworth, 1955), one sees, shortly after the change has occurred, the unusual picture of normal motor development with grossly defective concentration and interest in surroundings, indicating severe mental deficiency.

Within the field of motor development itself there are occasionally certain unusual variations. Normally a child learns to sit before he creeps. I have seen the reverse happen in a child who had been brought up in an institution, and who presumably had never been given any chance to sit. One commonly sees dissociation between the sitting and standing development: for instance, an 8-month-old child is seen to sit securely, like an average child of the same age, and yet to bear as little weight on the legs as a 2- or 3-month-old child. This is simply due to the mother not allowing him to bear weight on the legs in the erroneous belief that it will weaken or otherwise harm them.

Sometimes the age of sitting unsupported is quite average, while the child is unusually late in walking without help. In all other fields the child develops normally. For instance, a child sits unsupported at 7 months, but cannot walk without help till 18 months or later. As has already been stated, one sees this in cases of paraplegia. In most children, however, there is no organic disease. One factor may be lack of confidence or fear of falls. When a child refuses to walk without help for a long period (for four or five months, for example), simple

observation will show that his walking is maturing, and that as soon as he decides to walk alone he is walking well, like a child who has achieved the skill several weeks earlier.

Unusual but isolated advancement in motor development certainly does not indicate a high level of intelligence.

I saw a child sit without support at 4 months, creep (not crawl) at 4½ months, and pull himself to the standing position at 6 months. I expressed the opinion at that time that this was merely an isolated advancement, and that his I.Q. would not prove to be above the average. This was because he was in no way above the average in other fields of development. Although he subsequently walked without help at 8 months, his I.Q. at 5 years was 88. I saw another boy who walked unaided at 8 months, but was not advanced in other fields. His I.Q. at 6 years was 103.

Sphincter Control. Sphincter control is an unimportant field of development from the point of view of assessing a child's intelligence. It is delayed by a variety of organic and semi-organic conditions, and in particular by over-enthusiastic toilet training. In addition, there are very strong familial factors, unrelated to intelligence. When a child with average development in other fields is very late in acquiring control of the bladder, there is nearly always a family history of the same complaint. In mentally defective children one occasionally finds that sphincter control has been acquired at the usual time.

I would pay little attention to a history of unusually early acquisition of control, unless I were really satisfied that the control is truly voluntary, in that the child definitely asks for the chamber when he wants to void. It is easy to confuse the early 'conditioning', which is quite involuntary, with voluntary control.

Eyes, Ears, Manipulation. Unusual retardation in the use of the eyes, ears and hands, in the absence of retardation in other fields, is very rare. It may occur in the presence of obvious physical defects—visual or auditory in the case of the special senses, or of myotonia or other mechanical disability in the case of the hands. Unusual advancement in these fields is of no prognostic importance, though special manipulative aptitude can sometimes be detected in the early months.

Chewing. I find that the age of beginning to chew (average 6 months) is a useful milestone of development, with little variation in children of average development, and invariable retardation in mental deficiency.

I know of only one variation from the average in children of normal development in other fields, and that is related to mismanagement, in the form of failure to give the baby solid foods at an age when he should be given them. When they are introduced some months later (at the peak of the period of negativism), refusal to chew may occur.

Social Behaviour. Isolated lateness in social responsiveness, such as smiling and taking notice, is extremely rare in early infancy. It could be due to a visual defect.

In older infants and young children it is not so rare. I saw a child who was suspected of mental deficiency, because of a complete failure to smile or show facial responsiveness, but found that she was an example of congenital facial diplegia (Möbius syndrome). A child first seen by me at the age of 4 years, and in whom the diagnosis was infantile autism, was said by his mother never to have shown any social responsiveness at all. Development in all other respects had been normal. His I.Q. was average. One sees children with relatively 'normal' development, but with defective concentration and interest (see above). This nearly always signifies mental deficiency.

Unusually advanced social development is a good sign of superior intelligence. It is possible that early smiling might be in part related to a child's pleasant personality, but there is no evidence to that effect. I have seen two children smiling in response to social overture in the first week, and vocalizing in the third week: they had I.Q.'s subsequently in the region of 140.

In later months, unusually good concentration, alertness, determination and interest in surroundings is an important sign of superior intelligence and much more important than advanced motor development. It is unfortunate that it is so difficult to assess it and convert the assessment into figures.

Speech Development. Delayed speech development in the absence of retardation in other fields is never due to mental deficiency. It may occur in children with average or superior intelligence. In the majority of such cases there is either a family history of similar lateness, or there is no discoverable cause. Einstein gave his parents grounds for concern because of his defective speech at the age of 4 years. He was still speaking indistinctly at the age of nine. Other causes of lateness in speech without retardation in other fields include deafness, high-frequency or otherwise. It is never due to 'laziness', and serious harm is done by advising parents to do nothing for such a child unless he

speaks properly. He does not speak because he cannot, not because he is too lazy to speak. I firmly believe that the statement repeated from textbook to textbook that delay in speech is due to parents and siblings doing things for a child before he asks for them is a myth. I very much doubt the truth of another oft-repeated statement, that lateness in speech is due to jealousy. All children are jealous, and as lateness in speech is common, it is indeed difficult to prove that lateness in speech is due to jealousy and not to something else. I would only go so far as to say that inability to speak may perhaps be a very rare result of jealousy, but that it cannot be proved. Lateness in speech is never due to 'tongue tie' or to cleft palate, though cleft palate may be associated with a low I.Q. and so with lateness in speech. In this case there would be retardation in other fields too.

Unusual advancement in speech is a reliable sign of superior intelligence. I have never seen it in a child of average intelligence.

The importance of relating the level of speech development to that of development in other fields has already been noted.

Summary and Conclusions

In assessing the development of an infant or young child one should always note the relationship of one milestone of development to another, in order to assess the rate of development, and the relationship of milestones in one field of development to those in another. Not infrequently development in one field is out of step with that in another. This might be termed dissociation. The reasons for this imbalance are discussed.

Isolated delay in motor development may occur without apparent reason, so that the child grows up to be perfectly normal. More often it results from a physical disability, in particular hypotonia or hypertonia. It never signifies mental deficiency.

Relative advancement in motor development in relation to other fields occasionally occurs in mentally defective children. Unusual and isolated advancement in motor development does not mean superior intelligence.

Retardation in social behaviour is of considerable prognostic significance, implying a poor prognosis for intelligence. The degree of retardation in a child with retardation in other fields is of great importance: only slight social retardation with severe motor retardation may occur in the presence of a severe mechanical disability, such as cerebral palsy, with an only slightly lowered intelligence. Advanced social development is a good index of superior intelligence, except that it is difficult to assess in figures.

Isolated delay in speech frequently occurs in children of normal or superior intelligence, and never means mental deficiency. Only moderate retardation in speech in the presence of severe retardation in other fields (as in cerebral palsy) excludes severe mental deficiency. Isolated advancement in speech is a good sign of superior intelligence.

Isolated delay in sphincter control is commonly associated with mismanagement or with familial factors, and is of no importance in developmental assessment. Advancement, relative or absolute, is of little value because of the difficulty in assessing its significance (i.e. whether the control is really voluntary and not mere conditioning).

Delay in chewing may result from mismanagement, and otherwise does not occur alone.

I wish to thank Arnold Gesell, who gave me the opportunity to learn about normal development in his Department.

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DYSMATURITY

BY

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History

The Scottish obstetrician Ballantyne (1902) seems to have been the first to call attention to dysmaturity. He described the dry, parched skin, the long nails, the paucity of the amniotic fluid, the presence of meconium in amniotic fluid, and the advanced ossification in the skull. He found the weight and length of these children to be nearly always above average.

Bossi (1907) gave a description of dysmature infants which in the main agrees with Ballantyne's, but he maintained that they have a reduced amount of subcutaneous fat and that therefore their weight is lower than might be expected.

Bäcker (1915) described dysmaturity and emphasized that dysmature infants are subnormal as far as fat and weight are concerned.

Then, for some time, no attention seems to have been paid to dysmaturity, until Runge (1939, 1942, 1948) gave a detailed description of the dysmature child. He also indicated a method of recognizing the condition in some cases even before delivery. He called attention to the fact that in some women who eventually are delivered of dysmature children the amount of amniotic fluid and concomitantly the circumference of the abdomen decreases successively before delivery. Runge considers dysmaturity to be a sign of placental insufficiency as regards the transport of oxygen as well as other substances. He made no chemical analyses and his conclusion was probably based on the presence of meconium in the amniotic fluid and the loss of weight of the child.

Although no further major studies have been published, it is obvious that German obstetricians have realized the difference between prolonged gestation and dysmaturity, as is evident from Martius' textbook on obstetrics published in 1943.

In other countries, dysmaturity does not seem to have been recognized until Clifford, in 1945, reported 46 cases; he has more recently (1951, 1953, 1954, 1957) described the syndrome and its clinical importance in detail. Like Runge, Clifford considers dysmaturity to be caused by a placental insufficiency and introduces the term 'placental dysfunction syndrome'. However, he has no further proof that a placental insufficiency is the cause of dysmaturity, but seems to base his conclusions on the same clinical grounds as Runge and finds support in Walker's work (1954) on prolonged gestation. Clifford's papers are of considerable importance because he classified dysmaturity in different stages and because he has made the dysmaturity syndrome known to pediatricians. Consequently, the condition has since been the subject of reports from several countries (Taylor *et al.*, 1952; Selander, 1954; Ravera and Bottinelli, 1955; Kunstadter and Schnitz, 1956; and others).

Present Investigation

Definitions. In this investigation, the duration of pregnancy is given in weeks calculated from the first day of the last menstrual period. Thus, for example, if a child is born in the 40th week, this implies that the pregnancy has lasted between 274 and 280 days. If the gestation time exceeded 294 days, we have called this prolonged gestation or prolonged pregnancy.

If the child showed the clinical syndrome which Clifford (1954) designates as the 'placental dysfunction' syndrome, known in German as 'überreif', we use the expression 'dysmaturity' without regard to the duration of pregnancy.

The term 'postmaturity', which is often seen in the literature, is avoided because some authors use it to denote prolonged pregnancy, others to denote dysmaturity, others again to denote both prolonged pregnancy and dysmaturity.

Material. An investigation has been made of 1,171 newborn infants, all delivered at the Depart-

ment of Obstetrics, University Hospital, Lund, between January 1, 1956, and March 31, 1957.

Only during the later part of the investigation were all children born classified according to dysmaturity. The material was selected, in so far as mostly children with prolonged gestation were included. The selection in these cases was always made before the children were born.

The infants were classified, largely according to Clifford's classification, the day after delivery. This was done by only one of us, who at that time had no information concerning the mother, the duration of pregnancy, the delivery, the amniotic fluid or the placenta. Thus the classification was made only on the basis of inspection and observation of the naked infant.

Normal and premature infants without signs of dysmaturity have been grouped in Stage 0.

Stage 1 corresponds to Stage 1 of Clifford. The skin is cracked, parchment-like and peeling and the arms and legs are thin. The infants are more awake and alert than usual but they may have respiratory distress and a tendency to vomit. The bones of the skull are harder than is ordinarily found.

If the clinical picture just described was less pronounced and there was doubt whether to classify the infants as normal or dysmature, they were placed in Stage 0-1.

Infants who exhibited the signs attributed to Stage 1 in a very marked degree, have been grouped in Stage 2. In addition, the trunk was thin in these cases. In Stage 2, Clifford includes meconium staining of the amniotic fluid, but as the examining doctor did not have any knowledge of the amniotic fluid, this sign was not taken into account in grouping the infants. However, they all had greenish skin, umbilicus or nails. The amount of meconium needed in the amniotic fluid to stain the infants is very small, as shown by Desmond *et al.* (1956). This can also be deduced from the fact that in only half of our Stage 2 cases was meconium staining of the amniotic fluid noted at the time of delivery. Some of the infants also produced meconium stained vomit.

Stage 3 corresponds precisely to that of Clifford. In these infants the trunk and extremities are strikingly thin, moreover they have a rather pronounced dystrophic appearance. The skin peels off in large flakes. The nails and the skin are yellowish in colour.

Great care was taken in order to obtain as reliable information as possible about the time of gestation. Most of the mothers were under observation by the staff during pregnancy and, after labour, their menstrual history was examined in detail by us. Only cases with a regular menstrual cycle have been included and any case in which the duration of pregnancy was at all doubtful has been rejected in the calculation of the gestation time.

Blood samples from the newborn infants were taken from the umbilical cord, which was clamped in two places immediately after delivery. Blood was drawn from either the vein or the arteries and mixed with heparin or sodium oxalate. If not indicated otherwise in the tables, the blood was always drawn from the vein.

The investigation was in two parts, the first covering the period from January 1 to October 31, 1956, and the second from November, 1956, to March 31, 1957. During the first part, 581 infants were investigated in the manner outlined above. However, the series was considered too small and therefore another 590 infants were studied. As both parts of the investigation have given the same results, no detailed statistical analysis of the two series is necessary.

Frequency. Only a few reports on the frequency of dysmaturity are available. Selander (1954) gives a figure of 12·0% from a study of 1,330 infants. If the infants were born more than four days after the calculated date, 20·3% displayed the syndrome. Taylor *et al.* (1952) stated that the incidence of yellow vernix not associated with haemolytic disease —that is, dysmaturity Stage 3, was 1·2%. Ravera and Bottinelli (1955) report that 2·25% of their infants were born more than 14 days after term and often had symptoms of dysmaturity (in 38 out of 42 cases). Kunstadter and Schnitz (1956) investigated 247 infants with a gestational age of 294 days or more and among these found 11 infants showing clinical symptoms consistent with dysmaturity; this gives a figure of 0·4% for infants delivered liveborn. Hinselmann (1957) in 5,258 deliveries had 600 infants with a gestation time of more than 294 days and among these were 42 infants with all or nearly all the signs of dysmaturity—that is, 7·0% of those with prolonged gestation and 0·8% of all the deliveries.

The frequency of dysmaturity in our material is shown in Table 1. The calculation of the frequency has been made only for the period when all of the infants delivered were classified.

TABLE 1

STAGE AND PERCENTAGE DISTRIBUTION OF DYSMATURITY IN 444 NEWBORN INFANTS

Stage of Dysmaturity					
0	0–1	1	2	3	1–3
58·6%	24·8%	14·9%	1·6%	0·2%	16·7%

Thus, the frequency of dysmaturity in our material is 16·7%. The advanced Stages 2 and 3 were only seen in 1·8% of the newborn infants.

Gestation Time. Runge, and later Clifford, pointed out that dysmaturity is usually associated with prolonged pregnancy, but that it may be present even in infants born before term. Selander (1954) gives a dysmaturity frequency of 2·4% for infants born two to three weeks before term and a frequency of 1·1% for infants born more than three weeks before term.

Our material consists of 968 cases (Table 2).

TABLE 2
DISTRIBUTION ACCORDING TO GESTATION TIME (968 CASES)

Stage of Dysmaturity	Duration of Pregnancy in Weeks								
	36	37	38	39	40	41	42	43	≥44
0	3	9	21	103	141	149	42	14	11
0–1		1	5	25	57	77	41	9	8
1	1		2	13	47	61	50	26	12
2				1	2	8	13	6	10
Total	4	10	28	142	247	295	146	55	41

Two hundred and three cases have been excluded because, as already mentioned, the gestation time was uncertain. It should be noted that the frequency displayed in Table 2 does not give a true picture of the dysmaturity distribution as sometimes only infants of mothers with a gestation time of 41 weeks or more were investigated. Thus, the frequency distribution has been somewhat shifted towards the right—that is, towards prolonged gestation. However, the table clearly shows the increased frequency of dysmaturity with increasing gestation time, but it also shows that most of the infants with Stage 2 dysmaturity are born within 294 days.

Parity of Mother and Sex of Infant. Several investigators have shown (Rütte, 1949; Hosemann, 1948; Clifford, 1954; Lindell, 1956; Strand, 1956) that the increase in infant mortality observed in prolonged pregnancy only refers to primiparae. It is, therefore, of interest to study whether dysmature infants are mostly born to primiparae or not. This information is presented in Table 3 together with the sex distribution of the infants.

If Stage 0-1 is included in the dysmaturity group, this syndrome is more frequent among primiparae than among multiparae. A statistical analysis shows that this difference is significant ($0{\cdot}01>p>0{\cdot}001$). With advancing stage of dysmaturity the frequency of boys dominates over that of girls. If again Stage 0-1 is included, this difference is statistically almost significant ($0{\cdot}02>p>0{\cdot}01$).

TABLE 3
SEX DISTRIBUTION AND DYSMATURITY AMONG PRIMIPARAE AND MULTIPARAE (1,171 CASES)

Stage of Dysmaturity	Primiparae		Multiparae	
	Boys	Girls	Boys	Girls
0	100	107	201	196
0–1	61	41	86	80
1	69	55	75	55
2	12	6	15	8
3			4	
Total	242	209	381	339

Age of Mother. Clifford stresses that dysmature infants born of elderly primigravidae must be watched with great care, since experience has shown that foetal morbidity and mortality are high in these cases. It is therefore of interest to study whether the frequency of dysmaturity also increases with the age of the mother. As seen from Table 4 in our material there is no increasing frequency of dysmaturity with advancing age of the mother.

TABLE 4
PERCENTAGE DISTRIBUTION OF MATERNAL AGE

Maternal Age	Stage of Dysmaturity			
	0	0–1	1	2+3
	%	%	%	%
<20	7·0	6·2	7·5	8·9
20–24	22·8	22·4	27·5	17·8
25–29	32·9	35·0	31·0	29·0
30–34	23·5	22·0	19·3	22·2
35–39	10·8	12·3	13·0	15·6
≥40	2·8	1·9	1·6	6·7

Weight of Infant. The growth of the foetus has been the subject of much speculation, particularly in the case of prolonged gestation. Solth (1947), Calkins (1948), McKiddie (1949), Hosemann (1952) and Lindell (1956) state that growth slows down towards the end of pregnancy and then become almost stationary or at least increases very little as gestation proceeds. Some authors (Rathburn, 1943; Freudenberg, 1950) even state that in prolonged gestation the foetus will lose weight. Table 5 gives the weight of the infants for the 921 cases in which the gestation time was between 39 and 44 weeks.

TABLE 5
MEAN WEIGHT IN G. AT TERM AND IN PROLONGED PREGNANCY (921 CASES)

Duration of Pregnancy in Weeks	Stage of Dysmaturity			
	0	0–1	1	2+3
	g.	g.	g.	g.
39	3,320	3,425	3,118	2,600
40	3,440	3,363	3,332	3,140
41	3,675	3,597	3,423	3,230
42	3,708	3,677	3,649	3,233
43+44	3,819	3,761	3,561	3,603

Two curves are given in Fig. 1, one corresponding to Stages 0 and 0-1 considered together, the other to Stages 1, 2 and 3, also considered together. Fig. 1 shows that the mean weight of the normal infants increased continuously from the 39th to the 43rd and 44th week and that this increase was of the same magnitude each week. The mean weight of the dysmature infants was at 39 weeks already some 200 g. less than the mean weight of the normal infants but showed a similar weekly increase from the 39th to the 44th week.

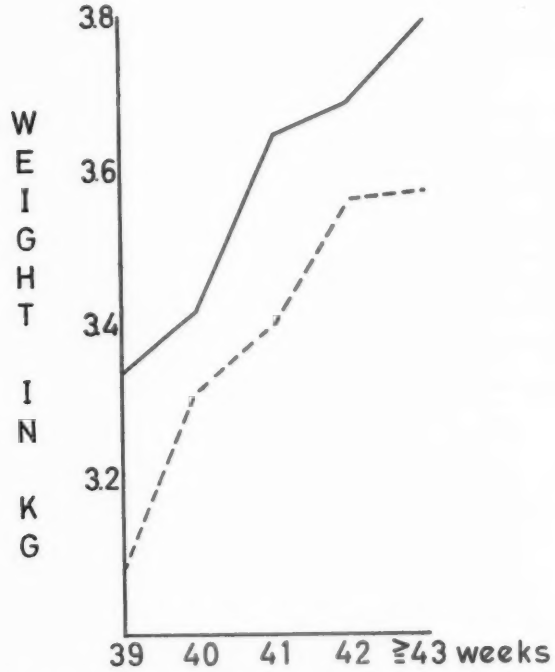

FIG. 1.—Weight curves of normal and dysmature infants.
———— Normal infants, Stages 0 and 0·1
— — — — Dysmature infants, Stages 1, 2 and 3

From a consideration of the gestation times in Table 2 and the weight curves in Fig. 1 two important conclusions can be drawn:

1. Although the frequency of dysmaturity is increased in prolonged gestation, it is not caused by prolonged gestation since evidence of dysmaturity is already manifest before term.

2. Although both normal and dysmature infants increase in weight with increasing gestation time, the difference in the weight curves can explain the apparent decrease in weight in prolonged pregnancy observed by other authors. Because of a steadily increasing proportion of dysmature infants in prolonged pregnancy, the percentage of the normal infants with high weight is gradually reduced, whereas the percentage of the dysmature infants with small weight gradually increases. This causes a flattening of a growth curve which includes all the infants. With great foresight this explanation was hypothetically proposed by Clifford (1957).

The reduced weight which the dysmature infants show as compared with the normal ones indicates insufficient nutrition during a relatively extended period of time, as would be expected in the case of placental insufficiency.

Length of Infant. Most of the above-mentioned authors who have studied the weight of the newborn infant have also studied the length and found that it increases up to and including the 43rd week.

This is confirmed in Table 6 which shows that, according to our data, the infant's length increases irrespectively of dysmaturity until and including the 43rd week. Thus, dysmature infants are of normal length but reduced weight. However, it should be remembered that it is difficult to measure the length of the newborn infant with a satisfactory exactness. The reduction in length which is suggested in the 44th week may not be real because the material is small and only includes 40 infants, and furthermore, in spite of our precautions, the true gestation time may, in some cases, be only 40 weeks instead of 44.

TABLE 6
INFLUENCE OF GESTATION TIME AND DYSMATURITY ON MEAN LENGTH OF INFANT

Gestation Time in Weeks	Stage of Dysmaturity			
	0	0–1	1	2+3
	cm.	cm.	cm.	cm.
37	46·6	47·5	—	—
38	48·8	47·9	50·5	—
39	49·5	49·5	49·0	48·0
40	49·7	49·6	49·6	50·0
41	50·8	50·5	50·3	50·1
42	50·6	50·9	51·1	49·7
43	51·7	51·4	51·0	52·0
≥44	50·2	50·6	51·0	51·1

Oxygen Saturation in Cord Blood. The oxygen saturation in the cord blood during prolonged gestation has been the subject of much discussion. Walker and Turnbull (1953) claimed that the oxygen saturation in the cord blood decreases with advancing gestation time in prolonged pregnancy. However, the number of infants studied was small. Minkowski *et al.* (1953) support Walker's thesis although they find exceptions. MacKay (1957) in a recent study, like Walker's, also from Scotland, of 240 infants, reaches the same conclusion as Walker and Turnbull (1953). But MacKinney *et al.* (1955) studying cord blood oxygen saturation in 594 infants did not find significant differences between mature

infants and infants with prolonged gestation. Rooth and Sjöstedt (1957b), investigating 363 infants, found no changes in the oxygen saturation from the 39th week to the 43rd week.

As far as we know, the oxygen saturation in cord blood has not been studied before in relation to dysmaturity, although Runge and most subsequent authors on dysmaturity have considered dysmature infants to be hypoxic.

The oxygen saturation, measured with a Brinkman haemoreflector in the manner already described by Rooth and Sjöstedt (1955) has been measured in the umbilical vein in 210 infants and in the arteries in 165 infants in our series (Table 7).

TABLE 7
MEAN OXYGEN SATURATION IN PER CENT IN UMBILICAL CORD BLOOD

		Totals	Stage of Dysmaturity			
			0	0-1	1	2
Vein	Number	210	104	35	59	12
	HbO_2		63·7%	58·6%	56·9%	51·1%
Artery	Number	165	79	29	47	10
	HbO_2		38·7%	34·7%	34·6%	24·3%

The oxygen saturation decreases both in the umbilical vein and in the arteries with advancing stages of dysmaturity. Thus, according to our results, in prolonged pregnancy the cord blood oxygen saturation is decreased only if the infant also is dysmature. An infant with no signs of dysmaturity will retain its oxygenation in spite of a prolongation of pregnancy beyond term.

These observations could explain the differing results obtained by the various authors studying the oxygen saturation in the cord blood of infants in prolonged gestation. If the number of infants studied is small, as in Walker's report, the percentage of dysmature children may be much higher than if a sufficiently large number of cases had been studied. Furthermore, there may be a notable difference in the frequency of dysmaturity in different countries.

Haemoglobin in Cord Blood. Walker and Turnbull (1953) found that from the 40th to the 43rd week the amount of haemoglobin in cord blood increased considerably and interpret this as a compensation for the decreasing oxygen saturation. Marks *et al.* (1955) and Rooth and Sjöstedt (1957a) could not confirm these results, both groups finding no increase in the haemoglobin in cord blood during prolonged gestation. MacKay found a slight rise with increasing maturity but the results tended to agree with the results of Marks *et al.*

No studies are available regarding the influence of dysmaturity on the cord blood haemoglobin. We have measured this in 885 infants (Table 8). The technique has been described earlier by Rooth and Sjöstedt (1957a).

The haemoglobin values rise with advancing signs of dysmaturity and this rise is already evident in the intermediate group, Stage 0-1. This increase of haemoglobin in dysmature infants suggests that, *in utero*, they were hypoxic, but it may be only a sign of haemoconcentration.

TABLE 8
MEAN HAEMOGLOBIN IN G. PER 100 ML. UMBILICAL CORD BLOOD (885 CASES)

	Stage of Dysmaturity			
	0	0–1	1	2
Number	450	205	194	36
Haemoglobin ..	16·1	16·7	16·9	17·0

Plasma Pentoses. The concentration of pentoses in plasma has been studied by Green and his collaborators, among others. Green *et al.* (1949) noted a significant rise in the plasma pentose fractions in battle casualties and believed this to be the result of ischaemia in the injured tissues. In the pregnant woman an increase in the plasma pentose fractions has occasionally been noted. Green *et al.* (1951) consider this to be due to a relative uteroplacental ischaemia.

Using the method of Mejbaum (1939) as modified by Green *et al.* (1951), we have measured the plasma pentoses in the cord blood of 198 infants (Table 9).

The plasma pentoses increase with advancing signs of dysmaturity. This probably indicates a progressive ischaemia and therefore supports our results on the analyses of the oxygen saturation and the haemoglobin in the cord blood.

TABLE 9
MEAN PLASMA PENTOSES IN MG. PER 100 ML. UMBILICAL CORD BLOOD (198 CASES)

	Stage of Dysmaturity			
	0	0–1	1	2
Number	92	35	58	13
Pentoses	4·6	5·0	5·6	6·5

Protein-bound Hexoses. For more than 50 years the protein-bound polysaccharides in serum have been studied mainly in connexion with diabetes mellitus. Abnormally high values have been found in a number of different pathological conditions. However, no final explanation for this abnormality has been found (Keiding, 1957). The

most commonly accepted explanation (Greenspan *et al.*, 1951) is that the protein-bound hexoses indicate tissue destruction. We have measured the protein-bound hexoses in the cord blood of 246 infants and our results are given in Table 10.

The protein-bound hexoses increase with advancing signs of dysmaturity. Even if no definite explanation for this can be given, it points to an increasing pathological process in the infant or in the placenta.

TABLE 10
MEAN PROTEIN-BOUND HEXOSES IN MG. PER 100 ML. UMBILICAL CORD BLOOD (246 CASES)

	Stage of Dysmaturity			
	0	0–1	1	2
Number	48	105	74	19
Hexoses	127·1	127·0	148·5	152·3

Bilirubin. Icterus neonatorum has been the subject of extensive investigations. Most of these studies have been devoted to the serum of the infant's blood after birth; however, others have been concerned with the cord blood as well. Davidson *et al.* (1941) report a mean value of 1·69 mg. per 100 ml. in 94 cases with a range of 0·42 to 3·9. As others before them they found that the higher the cord bilirubin the more intense became the icterus of the infant and the longer it lasted. Schick *et al.* (1942) compared the cord blood bilirubin in prematures, normal infants and overmatures (weight more than 3,800 g., length more than 52 cm.). With increasing maturity the bilirubin was reduced but the differences were so small that no conclusions could be drawn. We have analysed the bilirubin in the cord blood of 446 infants with Jendrassik's method (Table 11).

TABLE 11
MEAN BILIRUBIN IN MG. PER 100 ML. UMBILICAL CORD BLOOD (446 CASES)

	0	0–1	1	2
Number	218	115	103	10
Bilirubin	1·52	1·58	1·86	2·82

Although the differences are not large, there is a gradual increase in the bilirubin values in the cord blood with advancing signs of dysmaturity.

Non-protein Nitrogen. Reports on the NPN in cord blood have been published by Hellmuth (1924), Naeslund (1931), Slemons (1919), Pommerenke (1936) and Lichtenstein (1931). Their values vary between 25 and 40 mg. per 100 ml. of cord blood, and in the umbilical vein the values are slightly higher than in the arteries. Lichtenstein has correlated the NPN with the birth weight of the infant and shown that starting at a weight of 1,500 g., the NPN remains at the same level or 33 mg. per 100 ml. of cord blood.

McCance and Widdowson (1954) studied ten full term or post-mature infants all delivered by forceps. They analysed the urea and found a mean value of 39·9 mg. per 100 ml. of cord blood in six dysmature infants as compared with 30·9 in four normal infants. They took this as an indication that the urea concentration in cord blood is higher among dysmature infants and recommended further investigations.

We have analysed the cord blood of 804 infants for NPN (Table 12).

TABLE 12
MEAN NON-PROTEIN NITROGEN IN MG. PER 100 ML. UMBILICAL CORD BLOOD (804 CASES)

	Stage of Dysmaturity				
	0	0–1	1	2	3
Number	398	209	170	23	4
Non-protein nitrogen	28·8	29·4	29·7	34·7	37·0

The non-protein nitrogen in the cord blood also increases with increasing signs of dysmaturity. This is caused either by a placental insufficiency which prevents the foetus from excreting its NPN through the placenta or by an increase in tissue (notably placental tissue) destruction and subsequent increased production of NPN. Probably both of these mechanisms are of importance at the same time.

Albumin in Urine. Tests for proteinuria have been so consistently positive, especially during the second to fifth day after birth, that albumin in the urine is to be considered a more or less physiological constituent of the newborn infant's urine (Heller, 1913; Franz and Reuss, 1914; Ewald, 1916; Pfaundler, 1924). Ewald found that 75% of the urine samples taken from infants with birth weights below 3·5 kg. reacted positively to the albumin test; furthermore, 69% of the tests on larger infants were positive.

We have tested the urine for albumin using Heller's test on specimens from 577 newborn infants (Table 13). These specimens were taken as early as

TABLE 13
FREQUENCY IN PER CENT OF ALBUMIN IN URINE (577 CASES)

	Stage of Dysmaturity			
	0	0–1	1	2+3
Number	114	208	217	38
Albumin	18%	29%	30%	63%

possible, always within the first three days of life. The urine of all infants with positive albumin tests showed a negative reaction within one week after birth.

The frequency of albumin in the urine of the newborn infant increases with the degree of dysmaturity, showing that these infants are also suffering from an impairment of the renal function.

Glycosuria. Hoeniger (1911) reports the frequent occurrence of reducing substances in infants after complicated deliveries. Lindig (1922) found this in only three cases out of 24 delivered by forceps.

We have, using the glucose oxidase reaction, tested the urine of 577 newborn infants shortly after birth (never later than the third day). (Table 14.)

TABLE 14
FREQUENCY IN PER CENT OF REDUCING SUBSTANCES IN URINE (577 CASES)

	Stage of Dysmaturity			
	0	0–1	1	2+3
Number	114	208	217	38
Reducing substances	0·9%	1·9%	5·1%	10·5%

The frequency of glycosuria also increases with the degree of dysmaturity. In the normal infant glycosuria is rare, but is present in about 10% of the dysmature infants in Stages 2 and 3. Sometimes these infants may even show a clinical picture which resembles diabetes, a case report of which has been presented by Engleson and Zetterqvist (1957).

Discussion

The present study shows the importance of distinguishing between, on the one hand, the gestation time of the infant—that is, whether it is prolonged or not, and, on the other, the state of the infant—that is, whether the infant is normal or dysmature.

We find no untoward effects on the infants due to the prolongation of pregnancy *per se*, but we do find considerable changes in dysmature infants. Unfortunately, this important fact does not yet solve the clinical controversy as to whether labour should be induced or not in a woman who carries her child beyond term. The answer is, of course, that labour should be induced if the infant is dysmature, but this cannot as a rule be verified until after the child is born. If the Ballantyne-Runge sign is present—that is, if the circumference of the abdomen is rapidly reduced late in pregnancy, the child is likely to be dysmature. Foetal electrocardiogram studies (Southern, 1957) also indicate a possible method of diagnosing dysmaturity before birth.

The clinical picture of the dysmature infant is distinct and can be recognized with a little training. It would be advantageous to register all the newborn infants according to dysmaturity. Thus, mortality and morbidity statistics on the neonatal period in different hospitals and countries would be more easily comparable.

Interpretation of Results

The reduced weight, the hypoxia, the increased haemoglobin, and possibly also the increased NPN, indicate a reduction in the diffusion capacity of the placenta. This reduction is probably caused by an ischaemia or destruction of placental tissue, as indicated by the increase in pentoses and protein-bound hexoses, and possibly also by the increased NPN. The increase in bilirubin may be a sign of the increased blood formation and a concomitant increased turnover of the haemoglobin pigments. It may also be due to hypoxic disturbances in the liver function, as the increased frequency of albumin in the urine might be a sign of hypoxic kidney function.

Summary

In order to prevent confusion between the terms 'prolonged pregnancy' and 'postmaturity' the term 'dysmaturity' is introduced to denote the placental insufficiency syndrome.

One thousand, one hundred and seventy-one newborn infants have been classified according to dysmaturity and studied from various aspects.

The frequency of dysmaturity in our series is 16·7% and increases with advancing gestation time; it is also higher for primiparae and male infants. Both normal and dysmature infants increase in weight during gestation, but from the 39th week onwards until delivery the dysmature infants have a mean birth weight 200 g. below that of normal infants. As dysmaturity becomes increasingly severe the oxygen saturation in the cord blood decreases, whereas there is an increase in the haemoglobin, in the plasma pentoses, in the protein-bound hexoses, in the bilirubin and in the non-protein nitrogen.

The more pronounced signs of dysmaturity are also allied to an increased frequency of albumin and glucose in the urine of the newborn infants.

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CONGENITAL INTERRUPTION OF THE AORTIC ARCH

BY

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Complete interruption of the aortic arch is rare, and so far only seven cases appear to have been recorded (Maud Abbott, five cases, 1927; Evans, one case, 1933; Sewart, one case, 1948).

Apart from the rarity of this condition, the present case is recorded because it emphasizes that the clinical recognition of the condition may be complicated where there is persistent patency of the ductus arteriosus, and when an interventricular shunt allows better oxygenated blood to reach the lower part of the body. The case also illustrates, by the coincidence of abnormalities representing disturbances at the same period of development and by the occurrence of a maternal illness at, or about, the same time, the theory that many congenital abnormalities are the result of arrests of development at critical periods of embryonic development.

In infantile coarctation the aorta narrows proximal to the entrance of the ductus arteriosus, and here the diameter of the vessel is less, and usually much less, than that of the subclavian artery. In consequence, the lower part of the body is almost entirely supplied during foetal life by blood from the right ventricle which reaches it *via* the ductus arteriosus. There is no stimulus to develop anastomoses between branches from the aorta above and those below the narrowing. After birth and with the closure of the ductus, the circulation in the lower half of the body is dependent on the flow through the coarctated part of the arch and becomes insufficient. In complete interruption of the aortic arch the lower part of the body is at all times completely isolated from the left ventricle and is supplied by blood from the right ventricle through the patent ductus arteriosus. After birth this is venous blood and even that is only available for the short period that the ductus remains patent.

Clinical History

The mother was 24 years old and her blood group was Rh positive. After a 39-week pregnancy, a baby boy was delivered normally, on December 9, 1956, weighing 2,700 g. He was the second child, the elder, being premature, weighed 1,050 g. at birth, but is at present alive and well.

On the fourth day the infant fed poorly from the breast and supplementary feeding was started. He was then slightly jaundiced. On the sixth day complete artificial feeding was necessary and the baby was tube fed. Later on the same day he appeared ill, was pale and shocked and had a slightly jaundiced appearance. There was no pyrexia or cyanosis. The respirations were grunting and laboured with marked abdominal breathing. The liver and spleen were both palpable. The umbilicus was healing satisfactorily and the fontanelle was not depressed. The heart sounds were normal and no murmurs were heard. There were widespread crepitations over the right lung. The haemoglobin was 80% (Sahli). A radiograph showed a large heart with a shadow on its right border. It was considered that there was some central consolidation of the lung and probably an aspiration pneumonia. Oxygen, 'alevaire' and 'crystamycin' (0·5 ml. twice daily) were administered. In spite of the fact that the infant had never fed satisfactorily the birth weight had not decreased and he now weighed 2,800 g. At 9.30 p.m. on the same day the infant's condition suddenly deteriorated and he died in a few minutes.

Necropsy

The body was that of a well-developed male infant. The skin and conjunctivae had an icteric tinge. There was no pitting oedema. On opening the chest a large heart, with a big right ventricle, occupied the major part of the front of the chest, compressing the left lung posteriorly. The venous drainage was normal. The right auricle was not dilated and opened by a normal tricuspid valve into the right ventricle. This valve showed several cherry red, pin-head-sized cysts on its auricular aspect, the so-called 'congenital cysts'. The right ventricle was large with well-developed muscular walls. There was a patent interventricular septal defect high up in the membraneous portion, measuring 3 mm. by 4 mm. The pulmonary outflow tract was prominent and a large pulmonary artery, normal in position and direction, proceeded from it, giving off a branch to each lung and then, without change in its diameter, continued through the widely dilated patent ductus, to become the descending aorta. This gave origin to the usual thoracic and abdominal branches and divided into the common iliac arteries. The left auricle was not dilated.

There was a defective interauricular septum due to an inadequate and fenestrated septum secundum. The persistently patent slit-like opening measured 9 mm. by 2 mm. The left auricle opened through a normal mitral valve into the left ventricle which was smaller than the right. The aorta originated from the left ventricle. It was a smaller vessel than the pulmonary artery and was guarded by three semilunar cusps normally placed. The coronary vessels arose normally. A normal innominate and left carotid vessel were present and the aorta terminated as the left subclavian artery. There was no communication or strand of fibrous tissue between it and the distal aorta (Figs. 1-2).

The left lung was compressed by the enlarged heart, but the right lung filled the pleural cavity well. The other organs were congested, but were not otherwise abnormal.

Histology

The left lung showed extensive areas of primary non-aeration with some vernix 'squames' and mononuclear cells with foamy cytoplasm. A similar reaction was present in the right lung and the changes in both were consistent with the clinical diagnosis of an 'aspiration pneumonia'. The liver showed focal areas of necrosis with some prominence of myeloid haemopoiesis in relation to the portal tracts. The adrenal had a nest of primitive neuroblasts which measured 1·6 mm. by 0·8 mm. Sections of spleen, thymus, pancreas, kidney and brain showed the changes of acute congestion.

Discussion

To understand the pathology of this condition the embryology should be considered. During the course of development six pairs of aortic arches develop but not all are present at any one time. The period of development of the aortic arches extends throughout the fourth week of intra-uterine life and their transformation mainly occupies the fifth to the seventh week. The first arch appears at the beginning of the fourth week. Second, third, fourth, fifth and sixth arches appear in rapid succession but by the sixth week, when the sixth arch has appeared, the first and second arches are beginning to atrophy. Only towards the end of the fifth week are all the arches open and even the first is atrophic when the sixth is developing. Normally the first, second and fifth arches disappear entirely. The common carotid vessels are formed from the third arches. The fourth left arch forms that part of the arch of the aorta between the origin of the left common carotid artery and the aortic end of the ductus. This is the site of the defect in the present

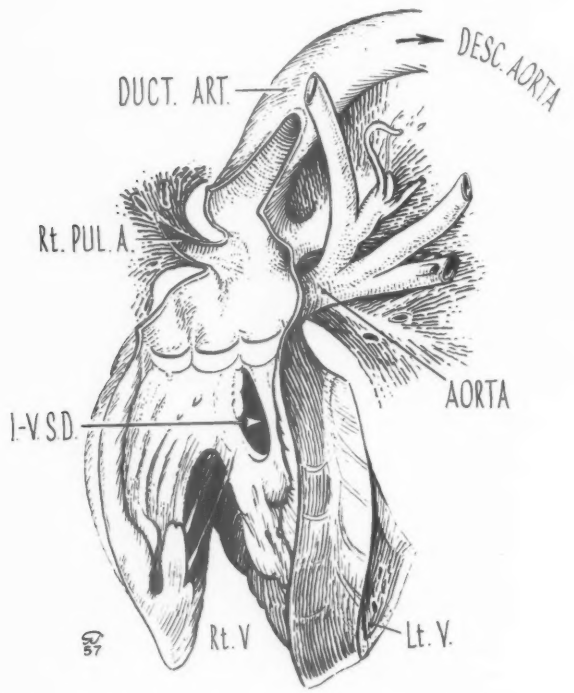

FIG. 1.—The heart showing the continuity of the descending aorta with the pulmonary artery and the interventricular septal defect. DUCT. ART., ductus arteriosus; DESC. AORTA, descending aorta; Rt PUL. A., right pulmonary artery; I-V.S.D., interventricular septal defect; Rt V., right ventricle; Lt V., left ventricle.

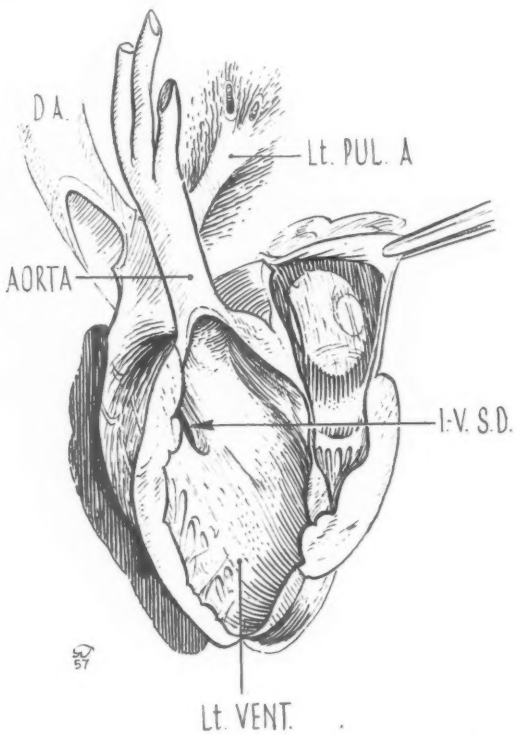

FIG. 2.—The left ventricle showing the aorta giving rise to the vessels of the head and upper extremities.
D.A., ductus arteriosus; Lt PUL. A., left pulmonary artery; I-V.S.D., interventricular septal defect; Lt VENT., left ventricle.

case, which essentially represents an involution of this portion of the fourth arch similar to the process normally affecting the first, second and fifth arches. Normally the portion of the same left arch distal to the origin of the subclavian artery joins the sixth arch to form the descending part of the arch of the aorta. The sixth arch forms both the pulmonary arteries and the ductus arteriosus, the latter closing in the neonatal period and its remains being identified as a fibrous band.

The interauricular septal formation begins in the fourth or fifth week of intra-uterine life and this is complete, apart from the post-natal closure of the foramen ovale, by the eighth week. In the first two weeks of neonatal life the foramen ovale closes in approximately 80% of infants. The interventricular septal formation begins in the fifth week of gestation and is completed by the eighth week.

In interruption of the aortic arch there is a complete disappearance of a portion of the fourth arch as well as the normal involution of the first, second and fifth arches. In infantile coarctation there is a failure of the structures derived from the arch in the region proximal to the ductus arteriosus to grow or to develop at the same rate as the rest of the vascular system at some period in foetal life.

The cause of any congenital defect is usually unknown, but at the present time environmental influences resulting from maternal illness or metabolic upsets during the first three months of pregnancy must receive most careful consideration. The period from the fourth to the eighth week is most critical with regard to heart development. Many of the known virus infections and obscure febrile illnesses have been implicated from time to time.

In the present case the defects would suggest some upset during the fifth to the sixth week of prenatal life. Careful investigation of the mother's health in the early months of her pregnancy was significant. Conception date could be more or less restricted to March 28, 1956. On April 28 and 29 the patient was ill with headache, vomiting, general malaise and slight pyrexia. The diagnosis of 'sinusitis' was made and only sedatives and analgesics were prescribed. The age of the foetus at this time was four and a half weeks. After a rapid recovery the mother's health was good until May 25, 1956, when she was confined to bed for a few days with a typical influenzal syndrome of headache, prostration, generalized muscle pain and vomiting. The foetal age at this time was eight weeks.

During the fourth-fifth week of prenatal life at a critical stage in the development of the aortic arches and the interauricular septum and just before the formation of the interventricular septum this foetus could feasibly have been subjected to some upset secondary to the maternal illness which resulted in the defects already described. The illness at the eighth week is probably of secondary importance as the cardiac structures are more or less established at this date.

Summary

A case is described of complete interruption of the arch of the aorta in a male infant dying aged 6 days. A patent interauricular and interventricular septum resulted in the absence of clinical cyanosis. The mother had a febrile illness at a critical period in the development of the aortic arch and cardiac septa in the foetus.

I wish to thank Mr. W. R. Sloan, consultant obstetrician, Lagan Valley Hospital, for permission to report this case; Dr. J. A. H. McClelland, the family doctor, for assisting with the ante-natal history; Dr. J. Edgar Morison for his help and advice; and Mr. G. A. Smith who made the illustrations.

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NORMAL DIAMETER OF THE HEART IN RADIOGRAPHS OF PRE-SCHOOL CHILDREN

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 20, 1957)

Over a period of several years children in the Oxford Child Health Survey had a chest radiograph taken at six-monthly intervals. As part of a genetic study measurements of the breadth of the heart shadow have been made on all those children who had brothers or sisters in the Survey. The chest radiograph was dropped from the routine examination some years before the end of the Survey but sufficient measurements have been taken to provide reasonable estimates of the average heart diameter of healthy children up to the age of 5 years. A summary of these measurements is presented here in the hope that it may provide a useful standard of comparison for children in whom enlargement of the heart is suspected.

Possibly the most usual radiographic criterion of normal heart size is the cardiothoracic index (total transverse heart diameter divided by internal diameter of the thorax), a value in excess of 0·50 being taken as *prima facie* evidence of enlargement. However, this ratio has certain disadvantages in early childhood when it is difficult to control the phase of respiration during exposure. In young children also the long axis of the heart is inclined at a much more shallow angle to the transverse axis of the thorax than in later life, so that healthy infants may exhibit a cardiothoracic index well in excess of 0·50. Bakwin and Bakwin (1935) concluded that age-standards for total transverse diameter provide as good a guide to normal heart size as the cardiothoracic index. This index has therefore not been calculated for the Oxford children and the present report is concerned only with absolute measurements.

All films were taken in the anterior posterior direction using a focal-film distance of 4½ feet (1·37 metres). The child was posed sitting in an erect position and an attempt was made to take the picture at full inspiration, although this was not always possible, especially with the younger children. Following Caffey (1945) heart diameter was taken as, 'the sum of the greatest perpendicular distance from the midline of the thorax to the right cardiac margin and the greatest distance from the midline to the left cardiac border'. Measurements were read directly from the film with a transparent rule marked in half-centimetre units.

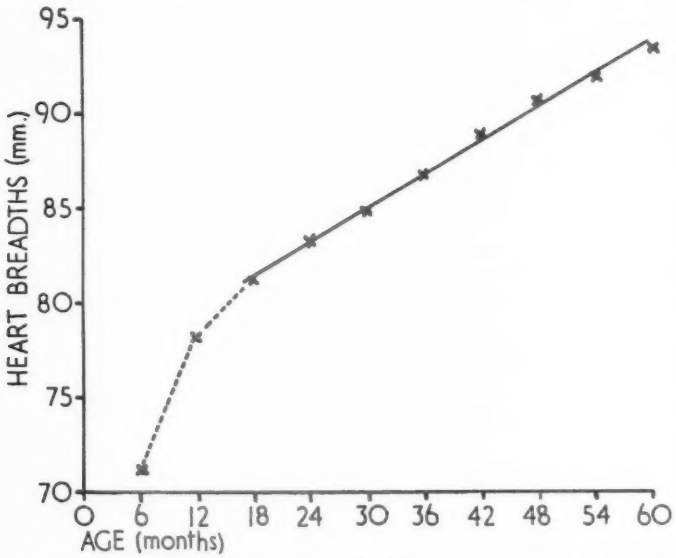

FIG. 1.—Mean radiographic heart diameter of Oxford children aged 6 months to 5 years: mixed series of boys and girls.

The apparent diameter on any individual film will, of course, depend to a considerable extent on the phase of the heart-beat at the moment of exposure. In view of the number of children measured at each age this source of variation has probably had a negligible effect on the averages, but, together with other errors, will certainly have inflated the estimated standard deviations and thus broadened the range of 'normal' diameter. This point is discussed below in connexion with Fig. 2.

Mean heart diameters at ten ages are shown in Fig. 1 for all children measured, without distinction of sex. It will be seen

hat the increase in heart diameter between the ages of 6 and 12 months is about 7 mm. and in the following six months about 3 mm. Thereafter the mean diameter increases very regularly at a rate of between 3 and 4 mm. per year. The linear correlation coefficient between age and mean heart diameter over the range 18 months to 5 years is +0·9986, a degree of correlation which justifies the use of a fitted regression line for estimating normal diameters in this age range. Such a line is also shown in Fig. 1.

The means and standard deviations at each age for boys and girls separately are shown in Table 1. Throughout the first five years of life the mean breadth is greater for boys than for girls by an amount which ranges from 2½ to 4½ mm. but which may reasonably be regarded, after allowance for sampling fluctuations, as a fairly constant 3½ mm. The standard deviation also tends to be greater for boys than for girls by an amount which, on average, is slightly more than proportional to the difference in means. However, for practical purposes, the coefficient of variation

$$\left(\frac{\text{standard deviation}}{\text{mean}} \times 100\right)$$

may be regarded as the same for each sex and, over the ranges 18 months to 5 years it may also be regarded as constant from age to age at about 6·2%.

These regularities in the data make it possible to draw a simple channel for the normal heart diameter of healthy young children, and this has been done in Fig. 2. The boundaries of this channel have been drawn at distances of two standard deviations above and below the mean, that is, they should include rather more than 95% of measurements based on individual films of healthy children. In particular, rather less than 1 in 40 radiographs of

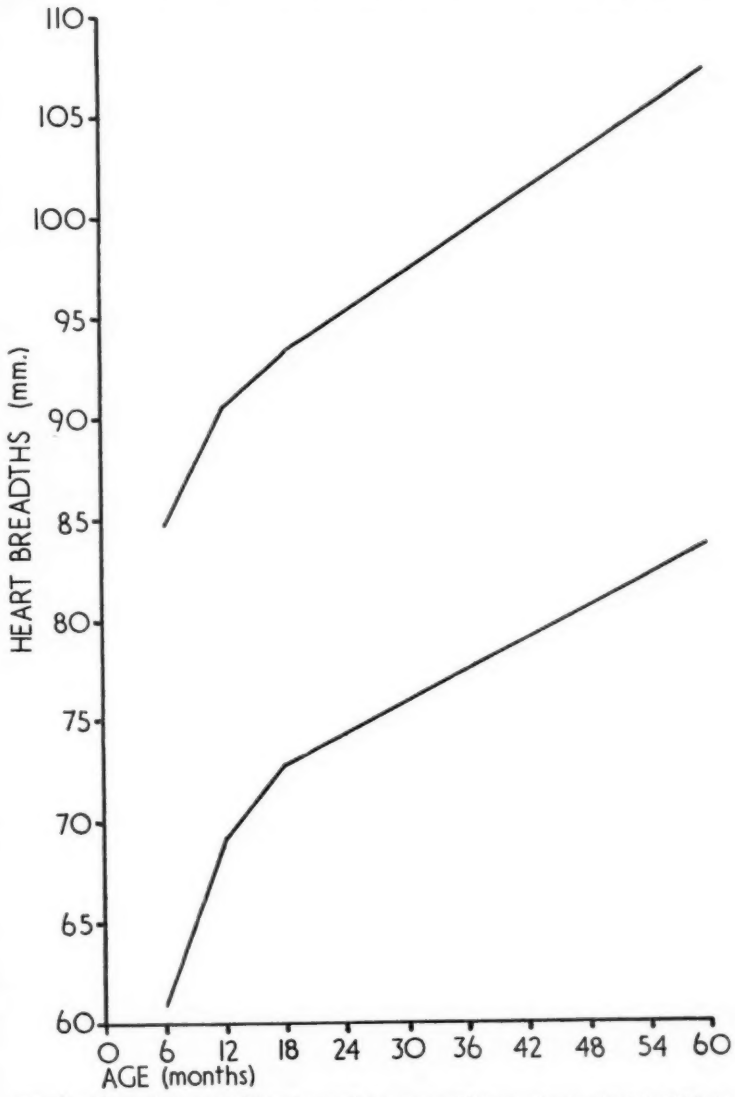

FIG. 2.—Normal channel of heart growth in young children. Approximately 95% of films of boys taken under the stated conditions should yield measurements between these limits. To compare a girl's heart diameter with these standards first add 3½ mm.

TABLE 1

MEAN AND STANDARD DEVIATION OF RADIOGRAPHIC HEART DIAMETER OF OXFORD BOYS AND GIRLS AGED 6 MONTHS TO 5 YEARS

		Age in Months									
		6	12	18	24	30	36	42	48	54	60
Boys	No. measured	98	106	101	94	74	73	69	67	56	47
	Mean (mm.)	73·2	79·8	82·7	84·8	86·9	87·9	91·2	92·2	93·8	96·1
	Standard deviation	6·2	5·2	5·2	5·1	4·8	6·1	5·5	5·8	6·4	6·1
Girls	No. measured	104	113	102	97	85	83	74	67	60	60
	Mean	69·4	76·7	79·7	81·6	83·2	85·4	86·8	88·8	90·3	91·4
	Standard deviation	5·4	5·2	5·1	4·9	5·1	5·7	5·4	5·4	5·0	5·3

healthy children taken under the stated conditions should show a heart diameter greater than that indicated by the upper line. The figure has been drawn for use as a standard for boys, but it may also be used to assess girls' measurements if these are first increased by 3½ mm. The channel is strikingly wide: a heart diameter of 84 mm. could be regarded as just within normal limits both at 6 months and at 5 years. However, as stated above, the true range of variability will have been somewhat exaggerated as a result of certain errors inherent in the measurements. From calculations based on successive measurements of the same children it can be inferred that the channel might have been narrower by about one-fifth if the measurements from which it is derived has been free from error. If several films of the same child exhibit heart diameters outside the limits of Fig. 2, or with an average outside them, there is, of course, a much stronger presumption of abnormality than when an isolated film falls outside these 95% limits.

No attempt has been made here to incorporate an allowance for general body size, but it must be borne in mind that children who are markedly large or small for their age must be expected to have rather larger or smaller hearts. In the present study it has been found (on the basis of assessments combining successive measurements of the same children) that heart diameter at a given age is correlated with body weight to the extent of +0·437. There is also a normal tendency for large or small hearts to run in a family, the sib-sib correlation of heart diameter in the Oxford data (again based on a combination of successive measurements) being +0·367.

Bakwin and Bakwin (1935) have published radiographic measurements of the heart diameters of a group of New York children taken at monthly intervals during the first year of life. Their figures emphasize the relatively rapid growth of the heart during the earliest months of life: the average gain in the first six months was 19 mm. (from 49 to 68 mm.) compared with only 7 mm. (from 68 to 75 mm.) in the remainder of the first year. Thus the gain between the ages of 6 months and 1 year was the same as found in the present study, although the New York children (who were described as coming from 'very poor homes') had slightly narrower hearts on average than post-war Oxford children of corresponding age. (After allowing for a slight difference in magnification the margin is about 2 mm.) The heart measurements of Denver children given by Maresh (1948) for children from the age of 4 years onwards are based on posterior anterior exposures and therefore cannot easily be compared with the present series. However, they agree with the Oxford measurements in showing a greater average heart diameter for boys than girls at the ages of 4 and 5 years, and also a similar degree of correlation with height and with weight.

Summary

Measurements of chest films taken in the course of the Oxford Child Health Survey have been used to set up approximate standards of normal heart diameter for children aged 6 months to 5 years.

All the films used in this study were taken by Miss Eleanor Roberts and Miss Margaret Barnes. I am indebted to Dr. W. Pennybacker for advice on the measuring technique. The Oxford Child Health Survey is supported by a grant from the Medical Research Council.

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THE CHANGING AETIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN*

BY

JOHN LORBER

From the Children's Hospital, Sheffield

(RECEIVED FOR PUBLICATION SEPTEMBER 9, 1957)

In his Bradshaw Lecture for 1944, Professor Bruce Perry (Perry, 1944) reviewed the historical aspects of the aetiology of erythema nodosum and later Doxiadis gave a more detailed account in his monograph on the subject (Doxiadis, 1951). It has been shown that erythema nodosum is a hypersensitivity reaction and the main triggers which elicit this reaction are certain bacterial and fungal infections. The relative importance of the various aetiological agents is influenced by geographical and racial factors as well as by the age of the patient. Their importance may also vary from time to time. Erythema nodosum was often in the past thought to be a manifestation of rheumatic fever, but this theory has long been disproved. In this country, tuberculosis and beta-haemolytic streptococcal infections are the only known important factors in children.

In recent years, only two large series of cases have been published in Great Britain and both of these emphasized the overwhelming importance of recent tuberculous infection. Perry found that of 67 children with erythema nodosum seen in the Bristol region 50 (75%) were tuberculin positive and 29 (43%) showed evidence of active primary tuberculosis. Only 11 children had a clear-cut history of pharyngitis; nine of these were tuberculin negative and skin tests showed that four were sensitive to streptococcal mucoproteins. The incidence of tuberculous infection was even higher in Doxiadis' (1949) 100 children who were seen in Newcastle-upon-Tyne and in Sheffield between 1947 and 1949. All his patients were tuberculin tested and 88% were positive, and 59 (67%) showed evidence of active tuberculous infection. Tuberculous complications developed within three months after the appearance of the erythema nodosum in eight children. A possible streptococcal aetiology has not been excluded for Doxiadis' patients, as tests for evidence of recent streptococcal infection were not performed. It must be remembered, however, that in those days it was much easier to demonstrate tuberculous infection than streptococcal infection by laboratory means.

Present Investigation

Material. In view of the recent considerable decline in the incidence of childhood tuberculosis in our community (Lorber, 1953) it seemed of interest to review the cases of erythema nodosum in children seen in Sheffield in more recent years. For this purpose, the records of all the 89 children under 15 years of age who were found to have erythema nodosum and who attended the Children's Hospital, Sheffield, during a period of six years from January 1, 1951, to December 31, 1956, were used. Of these, 40 were under the care of Dr. T. Colver. In addition I obtained permission to include cases seen by Dr. R. R. Gordon of the City General Hospital, Sheffield, and by Dr. H. R. Vickers and Dr. I. B. Sneddon of the Department of Dermatology, the Royal Infirmary, Sheffield. These sources added a further 16 cases for study making a total of 105. No further cases have been found after searching the records of the various Sheffield Hospitals and of the Chest Clinic.

Age and Sex Incidence. Erythema nodosum was seen in four children under 2 years of age. There were three peak years with 12 cases at 2 years, 17 cases at 9 years and 11 cases at 10 years. Otherwise, the frequency of the condition was very similar at each year of life, with an average of six cases (Fig. 1). Twenty-seven (26%) children were under 5 years of age, 42 (40%) were between 5 and 10 years of age and 36 (34%) were 10 to 15 years of age (Table 1).

There were 48 boys (46%) and 57 girls (54%). There was an interesting and progressive gradient

* Based on a paper delivered to the Paediatric Section of the Royal Society of Medicine on April 26, 1957.

in sex incidence in different age groups (Table 1). Under 5 years of age there were more boys than girls

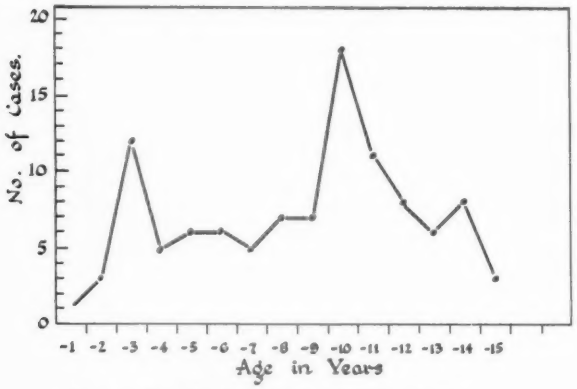

FIG. 1.—Age distribution of erythema nodosum.

TABLE 1
AGE AND SEX INCIDENCE
ERYTHEMA NODOSUM IN SHEFFIELD INVESTIGATION, 1951-56

Age in Years	Total	Females Number	Females %	Males Number	Males %
– 5	27	10	37	17	63
–10	42	23	55	19	45
–15	36	24	67	12	33
Adults	55	52	94	3	6
All ages	160	109	68	51	32

(17 boys to 10 girls), between 5 and 10 years of age boys were a little less often affected (19 boys to 23 girls) and between 10 and 15 years there were twice as many girls as boys (12 boys to 24 girls).

In 55 adult patients seen by Dr. Vickers and Dr. Sneddon during the same period 52 (94%) were women.

Aetiology

Tuberculosis. All children were tuberculin tested and a radiograph of the chest was obtained. The tuberculin tests used were the jelly test (without flour paper) and the Mantoux test in varying strengths from 1 to 100 T.U. old tuberculin (1/10,000-1/100).

A positive skin test was found in 65 children (62%) as a result of natural infection. Five other children were also tuberculin positive but these had recently been vaccinated with B.C.G. and form another group. Thirty-five children (33%) were tuberculin negative (Table 2).

TABLE 2
TUBERCULIN TEST REACTIONS IN CHILDREN WITH ERYTHEMA NODOSUM

Tuberculin Test Reaction	Number	%
Positive	65	62
Positive (B.C.G. vaccinated) ..	5	5
Negative	35	33
All cases	105	100

There was a decreasing incidence of tuberculous infection during the six years of this study. Whereas in 1951 to 1953, 73% of 49 children were tuberculin positive as a result of natural infection, in 1954 to 1956 this proportion fell to 51% of 56 cases. There was also a fall in the absolute number of tuberculin positive cases from 36 in 1951 to 1953 to 29 in 1954 to 1956 (Table 3).

TABLE 3
INCIDENCE OF TUBERCULOUS INFECTION IN CHILDREN WITH ERYTHEMA NODOSUM

Year	Number of Cases	Tuberculin Positive Number	Tuberculin Positive %	Active Tuberculosis Number	Active Tuberculosis %
1947-49*	100	88	88	59	59
1951-53	49	36	73	27	55
1954-56	57	29	51	19	34

* Doxiadis, 1949.

The incidence of tuberculous infection was practically the same in boys and girls (62%). Tuberculosis, however, was much commoner in younger than in older children. Of 29 children aged 2 to 5 years, 25 (86%) were tuberculin positive; of 52 under 9 years of age 37 (71%) and of 53 of 9 years or more only 28 (53%) were tuberculin positive (Table 4).

TABLE 4
INCIDENCE OF TUBERCULOSIS IN CHILDREN WITH ERYTHEMA NODOSUM ACCORDING TO AGE AND SEX

	0–8 Years					9–14 Years				
	All Cases	Tuberculin Positive		Active Tuberculosis		All Cases	Tuberculin Positive		Active Tuberculosis	
		Number	%	Number	%		Number	%	Number	%
Boys	30	21	70	17	57	18	9	50	8	44
Girls	22	16	73	13	60	35	19	54	8	23
Total	52	37	71	30	58	53	28	53	16	30

CHILDREN WITH ACTIVE PRIMARY TUBERCULOSIS. A positive tuberculin reaction does not necessarily indicate that the erythema nodosum was due to the tuberculous infection, unless tuberculin conversion coincided in time with the eruption and other possible causes were excluded. Unfortunately, in most cases there was no record of the tuberculin status before the skin eruption. It was possible, however, to divide the 65 tuberculin positive children into two groups: in 46 (43%) there was clinical and radiological evidence of a recent and active tuberculous process, and in the remaining 19 the only evidence of the tuberculous infection was the positive skin test.

The proportion of children with active primary tuberculosis was 55% in 1951 to 1953 (27 of 49) and only 34% (19 of 56) in 1954 to 1956 (Table 3). As might be expected, younger children with a positive skin test more often had an active tuberculous lesion. In children under 9 years of age 58% had active lesions as compared with 30% of all children aged 9 years or more. Among 35 girls aged 9 years or more only eight or 23% had an active tuberculous infection (Table 4). In this group there was a big difference between the incidence of active tuberculosis in the two sexes.

All the 46 children (25 boys and 21 girls) with definite active primary tuberculosis had non-calcified primary complexes or enlargement of the hilar lymph nodes in radiographs of the chest. In no case was the hilar enlargement bilateral. In 18 of those who had been followed up for a sufficient period calcifications were subsequently demonstrated. Significant contact with an active case of tuberculosis was either already known or was found to have occurred immediately prior to the onset of the erythema nodosum in 22 cases. In five cases, tubercle bacilli were cultured from gastric washings. This is a minimal figure, as children were often not admitted to hospital and gastric washings were not a routine procedure. Ten of the 46 are known to have developed important tuberculous complications within nine months of the eruption. These were tuberculous meningitis in three, bronchopneumonia in one, arthritis of the hip in one, pleural effusion in three and phlyctenular conjunctivitis in two (Table 5).

CHILDREN WITH INACTIVE TUBERCULOSIS. It is not possible to calculate precisely the expected incidence of positive tuberculin reactors in this group of 105 children based on the incidence in the general child population, as the information is not sufficient and the numbers are relatively small. It is likely, however, that the incidence of 18% who showed a positive tuberculin reaction as the only evidence of infection corresponds fairly well to that in the general child population. Seven of 52 (13%) were under 9 years of age, and 12 of 53 (23%) were over 9 years of age. There was only one child in this group who had definite enlargement of the hilar lymph nodes but he was known to be tuberculin positive 18 months earlier. None of these 19 children are known to have developed tuberculous illness of any type during the period of observation.

B.C.G. VACCINATED CHILDREN. Five children who gave a positive tuberculin reaction had been vaccinated with B.C.G. before the onset of the erythema nodosum. One of these, a boy of 14, was vaccinated nine months earlier at school and he converted two months later. His illness followed a sore throat and although his throat swab was negative when he was first seen, the antistreptolysin-O titre was 600 units. A radiograph of the chest was normal. The B.C.G. vaccination was clearly not responsible for his eruption, which was probably due to streptococcal infection.

In the other four vaccinated children the eruption occurred at about the time of tuberculin conversion, but an additional factor was present in three of these, so that the B.C.G. vaccination was not necessarily responsible for the attack. The father of one had active pulmonary tuberculosis and this 18-month-old child was not segregated from him during the period of vaccination. The child developed erythema nodosum only two weeks after vaccination. He then had a normal radiograph of the chest, but two years later a further radiograph showed a shadow consistent with a primary tuberculous complex. This child may well have had a recent virulent tuberculous infection which led to his erythema nodosum.

TABLE 5

TUBERCULOUS COMPLICATIONS IN 46 CHILDREN WITH ACTIVE PRIMARY TUBERCULOSIS

Meningitis	3
Bronchopneumonia	1
Hip disease	1
Pleural effusion	3
Phlyctenular conjunctivitis ..	2
Total	10 (22%)

Two 13-year-old girls had been vaccinated at school. One had already had an attack of erythema nodosum four years earlier and the fresh attack was preceded by a severe sore throat. When first seen her throat swab was negative, but an A.S.O. titre was not performed. She had a typical fresh B.C.G. lesion, and a radiograph of the chest was

normal. The other girl was vaccinated only three weeks before the erythema nodosum, but she already had a good B.C.G. lesion and gave a positive reaction to 10 units of O.T. A radiograph of the chest was negative. She did have a sore throat a week before the onset of the erythema nodosum, but her throat swab when first seen was negative. The A.S.O. titre was 200 units. The eruption cleared completely, but two weeks later a fresh extensive eruption developed without a preceding sore throat. This time beta-haemolytic streptococci were present in her throat swab. In these two girls either the B.C.G. vaccination or a streptococcal infection or both might well have been responsible for the eruption.

Finally, an infant aged 10 months had a mild eruption of erythema nodosum six weeks after vaccination without any other additional feature. This is the only child in whom B.C.G. was the only known predisposing factor, but streptococcal infection was not excluded by laboratory evidence.

Streptococcal Infection. Of the 35 patients whose tuberculin tests and radiographs were negative at the time of their erythema nodosum, 17 had a sore throat within two weeks before the eruption. Throat swabs were taken at the time of the child's first visit in 15 children, including 11 with preceding sore throats, and beta-haemolytic streptococci were grown in four. In addition, an elevation of the A.S.O. titre was found in six children whose throat swabs were negative or in whom swabs were not taken (titres of 200, 450, 600, 800, 900 and 2,000 units). A recent beta-haemolytic streptococcal infection was therefore demonstrated in ten of these 35 (Table 6). In 19 children in this group no investigations were undertaken to detect such infections. Among 11 children from whom were obtained both throat swabs for culture and blood for A.S.O. titre, there were only two who gave a negative reaction to both tests.

Unfortunately, in most of the tuberculous cases no further investigations were carried out after a positive tuberculin test and other evidence of active tuberculosis was found. Nevertheless, among the 65 tuberculin positive children the eruption was preceded by a severe sore throat in 15, and Lancefield group A beta-haemolytic streptococci were cultured from throat swabs in four of these. Another child had an A.S.O. titre of 500 units. As no throat swab was taken from 45 children and the anti-streptolysin-O titre was only estimated in one, the five proven cases of concurrent streptococcal infections represent a minimal figure. Four of the five had an active tuberculous lesion.

Among the 105 children there were, therefore, 35 (33%) who complained of a preceding sore throat; beta-haemolytic streptococci were found in their throat swabs in nine and a significant elevation of their A.S.O. titre was also found in nine patients. The total with proven streptococcal infection was 17 (16%) (Table 6).

TABLE 6

INCIDENCE OF STREPTOCOCCAL INFECTION IN CHILDREN WITH ERYTHEMA NODOSUM

Type of Case	Total	Pharyngitis	Positive Throat Swab or Elevated A.S.O. Titre*
Tuberculous ..	65	15	5
B.C.G.	5	3	2
Non-tuberculous	35	17	10
Total ..	105	35	17

* 200 units or more.

Rheumatic Fever. Only one child had coexistent rheumatic fever. This boy of 12 developed erythema nodosum and rheumatic fever with carditis following a streptococcal tonsillitis.

Other Diseases. In no child were other associated diseases detected, e.g., sarcoid or meningococcaemia.

Drugs. None of the children received sulphathiazole and no clear evidence is available that drugs played a part in provoking the eruption in any case.

Familial Factors. More than one case of erythema nodosum occurred in three families. In one, a girl of 11 years and a boy of 8 years had erythema nodosum at about the same time following sore throats. Both of these were known to have been tuberculin positive 18 months earlier. In the second the mother developed erythema nodosum before her 2-year-old boy. The boy had an active tuberculous infection which was probably contracted from a tuberculous neighbour.

More interesting is the history of the third family in which three children were affected in the course of six years. This is the only true example of familial susceptibility to erythema nodosum in this series.

The three children, twin brothers and a cousin, lived in the same house. All three were persistently tuberculin negative. One twin developed erythema nodosum at the age of 6, in 1950. The next episode occurred in January, 1953, when the second twin had erythema nodosum following a sore throat. He had beta-haemolytic streptococci in his throat. The first twin then had a second attack in December, 1954, without any apparent predisposing cause. Finally, their first cousin, a girl of 9 years, had erythema nodosum a further 15 months

later. She, too, had a proven beta-haemolytic streptococcal throat infection.

Relapses. Six children (5%) had a second attack after the eruption of the first attack had completely faded. Two children had their first attack before 1951 and four during the six years of this study. In three, the second attack occurred between three and five years after the first one. In the three others this happened within four weeks of the first crop. In only one child was active tuberculosis detected at the time of the first attack, but even she had a preceding sore throat. In none of the other cases did tuberculosis play a part, except that two had been vaccinated with B.C.G. not long before their second attack. It is of interest, however, that the twins quoted above, one of whom had two attacks, were subsequently vaccinated with B.C.G. without subsequent erythema nodosum.

Discussion

It is legitimate to conclude from these findings that although tuberculosis is still a very important aetiological factor in erythema nodosum in children, its importance is steadily decreasing. In the last three years little more than half the children had a positive tuberculin reaction and only one-third had active tuberculosis.

Tuberculosis was a far more important aetiological factor in young children among whom 71% had a positive skin test and most of these had active primary tuberculosis. These figures are in contrast with children over 9 years of whom only 30% had active primary tuberculosis.

As B.C.G. vaccinations are increasing in number, we shall have to think of it among the possible causes when confronted with a case of erythema nodosum.

We shall not know the true incidence of streptococcal aetiology until all cases are investigated routinely by throat swabs and the estimation of A.S.O. titres. When we do this we shall probably find many cases of erythema nodosum in which multiple factors operate. This was shown to some extent by the figures which have been presented. The concept of mixed infection or complex aetiology has previously been elaborated by Westergren (1945).

Holmdahl (1950) found in a series of 657 cases that the prognosis of primary tuberculosis was much worse in children with than in those without erythema nodosum. Our smaller series fully confirms his findings. It appears reasonable, therefore, to prescribe a course of treatment with isoniazid plus streptomycin or P.A.S. for children who show evidence of an active primary tuberculosis associated with erythema nodosum.

Summary

In a consecutive series of 105 children with erythema nodosum seen in Sheffield between January 1951 and December 1956, 65 (62%) were tuberculin positive as a result of tuberculous infection, five cases followed B.C.G. vaccination, and 35 (33%) were tuberculin negative.

There was a progressively falling proportion of children with a positive tuberculin reaction. Out of 49 children seen in 1951 to 1953, 73%, and out of 56 seen in 1954 to 1956 only 51% were tuberculin positive. An active primary tuberculous lesion was seen in 46 children (43%) in the whole series. The proportion was 55% in children seen during 1951 to 1953 and 34% in 1954 to 1956. Ten of the 46 children developed various forms of tuberculous diseases (apart from the erythema nodosum and the primary complex) during observation. In 19 children (18%) the only evidence of tuberculosis was a positive skin test.

Five children developed erythema nodosum after B.C.G. vaccination, and in four this occurred at the time of tuberculin conversion. Nevertheless, additional tuberculous or streptococcal infections were present in three of them.

Among 35 tuberculin negative children, 17 complained of a preceding pharyngitis and in ten laboratory evidence of a beta-haemolytic streptococcal infection was obtained; in 19 children no investigations were performed to prove a possible streptococcal aetiology. Such investigations were even less commonly performed in the 65 tuberculin positive children. Nevertheless the eruption was preceded by a sore throat in 15 and streptococcal infection was demonstrated in five. Among the 105 cases there were altogether 17 with a proven streptococcal infection.

Relapse of the erythema nodosum occurred in six cases and multiple cases occurred in three families.

I wish to thank Professor R. S. Illingworth for his criticism; Dr. T. Colver, Dr. R. R. Gordon, Dr. I. B. Sneddon and Dr. H. R. Vickers for permission to study their cases and the many family physicians who referred their patients to us.

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CLINICAL AND BIOCHEMICAL CHANGES DURING EXCHANGE TRANSFUSION

BY

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The development of exchange transfusion has greatly altered the prognosis of haemolytic disease of the newborn and the procedure is now accepted as being essential in cases of any severity. It is carried out wherever the criteria for operation are fulfilled and by operators of varying skill and experience. The difficulties associated with blood transfusion have received increasing attention in recent years, and its employment is beset with problems not only of cytology and serology but of microbiology, biochemistry, allergy, dynamics, religion and race. Some of these are greatly increased by the volume of blood used in exchange transfusion. Considering that the infant may be perfused with stored blood of altered chemistry in quantities of up to three times his own blood volume, it is surprising perhaps that it can be done at all. Hazards such as sepsis, air embolism, portal-vein thrombosis and perforation of the umbilical vein have been described, but are fortunately uncommon. Circulatory overloading is an ever-present danger in the profoundly anaemic infant, and it may be precipitated by conducting the exchange transfusion too rapidly. Deterioration and even death, however, may occur in infants whose pre-operative condition gave rise to no concern. Such clinical deterioration was observed in 40% of the cases transfused by Walker and Neligan (1955), and it did not appear to be related in any simple way to the baby's initial condition, to birth weight, to the technical difficulties encountered or to the rate of exchange. Moreover, Walker (1955) was led to believe, from inquiries received by him, that unexpected death was commoner over the United Kingdom than he had previously thought. Signs of clinical disturbance which had been observed by one of us (J. W. F.) during exchange transfusions at the Simpson Memorial Maternity Pavilion, Edinburgh, between 1948 and 1953, prompted us to undertake a joint study of a series of infants during operation.

Plan of Investigation

In the belief that analysis of serum taken during exchange transfusion would reflect the ability of the newborn infant suffering from erythroblastosis foetalis to maintain a normal serum electrolyte picture, electrolyte balance with reference to calcium and potassium ions has been evaluated.

Methods

Clinical. The technique of exchange transfusion was essentially that described by Farquhar and Lewis (1949). A careful clinical record was kept during the transfusion. This included recording the volume of blood exchanged, heart rate, and the occurrence of clinical incident. The exchange was carried out slowly, and if the patient was not tolerating the procedure the apparatus was flushed with saline and the infant rested for 5–15 minutes. As many as three or four rest periods were necessary for readjustment in some of the more seriously disturbed babies.

Specimens of blood were collected at regular intervals during transfusion. In the first series of cases studied blood was collected at intervals immediately before the administration of calcium gluconate. In the second series blood was collected at intervals immediately before and after the administration of calcium gluconate. In the event of any abnormal incident occurring during transfusion, specimens of blood were collected immediately. During specimen collection, contamination of blood samples with the contents of the polythene catheter was avoided by the following procedure. A few millilitres of the infant's blood was sucked into the syringe and rejected into the waste bucket. By this means any residual donor blood was removed from the polythene catheter. The actual blood specimen was then withdrawn and placed in a centrifuge tube. Specimens were centrifuged soon after clot retraction, and the sera were stored in the refrigerator until analysis.

Analytical. Sodium and potassium were determined by means of the flame photometer; protein by the micro-Kjeldahl procedure (King, 1951); total calcium by the method of Sobel and Sobel (1939), with the modification that the serum was ashed prior to oxalate precipita-

tion in order to eliminate citrate; citric acid by a method devised by one of us (H. S.), the principle depending on the oxidation of citrate to acetone with vanadate, and the subsequent distillation of the liberated acetone into an alkaline solution of salicylaldehyde, forming a coloured complex which was measured colorimetrically.

Simultaneous electrocardiography would have been of much value, but unfortunately no suitable machine was available.

Patterns of Clinical Disturbance Observed

A quite unexpected near-fatality observed during exchange transfusion in 1953 finally provoked these observations.

A mature female infant of 8 lb. 6 oz. birth weight, second of a family, had a cord haemoglobin of 17·4 g. per 100 ml., a cord serum bilirubin of 3 mg. per 100 ml., and a strongly positive Coombs test. There was no splenomegaly and the liver was judged to be normal. Influenced only by the bilirubin level, it was decided to carry out an exchange transfusion. No trouble was anticipated. Aliquots of 10 ml. of blood were exchanged at an average time interval of one minute. Calcium gluconate 0·1 g. was injected at intervals of 100 ml. The operation proceeded smoothly until 430 ml. had been exchanged, when the infant suddenly collapsed and became pale and unresponsive. The heart rate increased from 132 to 152 beats per minute. Calcium was given without effect. Glucose 20% solution was given intravenously quite empirically in a dosage of 6 ml. The baby appeared to improve, but on resumption of the exchange she collapsed again. Glucose was given once more with less convincing effect. The transfusion was then continued much more cautiously and in negative balance to a total of 740 ml.

Of the 19 infants studied, one died during transfusion. Six others showed some clinically recognizable disturbance at some stage of the procedure. The remaining 12 infants were normal throughout. Different patterns of clinical disturbance were observed, and a description of these is essential to the further understanding of the investigation.

Distal Cyanosis. Two babies produced an alarming clinical picture which, probably as a result of modification in technique, was not observed in subsequent transfusions. In both cases (F and R) difficulty was experienced in withdrawing blood during the first 100 ml. of blood exchanged. Persistent efforts were made to overcome this by partial withdrawal and reintroduction of the catheter. In both cases the catheter tip was advanced along the umbilical vein for about 11 cm. and repeatedly encountered some resistance, which was thought at the time to be within the portal circulation. Both babies developed a deep cyanosis of the lower half of the body, and this contrasted dramatically with the pallor of the upper half. Increased venous filling became apparent over the trunk and the veins were noted to drain superiorly. No pitting oedema of the legs was noted. The symptoms disappeared spontaneously in about half an hour. This phenomenon has been designated 'distal cyanosis'.

Retching. Three infants (B, H and J) suffered from repeated retching of mucus. This is a common observation during exchange transfusion, and because of this milder degrees have not been recorded.

Shock. Three infants (B, F and M) presented a clinical picture to which the term 'shock' has been loosely applied. These infants showed some or all of the following features in varying degree. After crying lustily initially on restraint, they became unduly quiet and pale during operation. At least one infant was so pale that the possibility of internal bleeding was considered. The babies were cool and their abdomens became distended. The latter was not due to liver enlargement. They became 'hypotonic' and unresponsive. Little change in heart rate was observed and there was no increase in venous pressure. Case B showed this clinical picture within the first 100 ml. of blood exchanged, but survived an exchange of 600 ml.

Cardiac Failure. Signs of congestive heart failure appeared in one case only (J). This baby suffered from repeated retching during the exchange of the first 200 ml. of blood. He remained irritable, and after an exchange of 700 ml. he was beginning to show evidence of deterioration. Respiration became a little distressed and dyspnoea was obvious after 800 ml. of blood. At this stage the heart rate had increased from a resting rate of 138 to one of 164 per minute. The venous pressure in the portal circulation rose from a resting level of 7·5 cm. to 30 cm. The baby was a little cyanosed, the superficial veins became more obvious and the liver enlarged. Unfortunately the blood specimen taken at this point was lost, but the values found in the preceding one were coexistent with the signs of early cardiac failure.

Acute Non-fatal Collapse. One infant (R) collapsed suddenly and unexpectedly, but he fortunately recovered. He had been well until 470 ml. of blood had been exchanged. He then retched and became apnoeic and deeply cyanosed. The heart sounds were faint and the rhythm was irregular, but his condition gradually improved over a ten-minute period. This has been broadly

termed 'acute non-fatal collapse'. Samples of this infant's blood were being taken only at intervals of 200 ml., and the nearest specimen to the incident was taken after 400 ml. of blood had been exchanged.

Death. One infant (I) died during operation. This infant was born with assistance by the breech, was limp at birth and was covered with yellow vernix. The cord haemoglobin was 9·8 g. per 100 ml. and the serum bilirubin 3·5 mg. per 100 ml; there were very many nucleated red cells in a peripheral blood smear and the Coombs test was strongly positive. Both liver and spleen were palpably enlarged. Apart from pallor no abnormality was noted until the infant collapsed and died at 500 ml. Necropsy revealed considerable bilateral tearing of the tentorium cerebelli, and a subtentorial subdural haematoma of such size that the medulla oblongata was flattened antero-posteriorly. Considerable intraperitoneal haemorrhage was also noted. No source of bleeding was found to explain this other than some haemorrhage around the umbilical vein in the region of the anterior abdominal wall. Although no perforation was found, this seemed to be the likely source of intraperitoneal blood loss. The pathological opinion was that the subdural bleeding alone, or with the intraperitoneal haemorrhage, provided adequate reason for the baby's death.

Relationship of Behaviour to Severity of Disease, Birth Weight, Volume and Speed of Exchange

The severity of the haemolytic disease process was classified arbitrarily into three grades: mild (+), moderate (++) and severe (+++) (Tables 1 and 2). In all cases a Coombs test was positive. The mild cases had a cord haemoglobin value greater than 14 g. per 100 ml. and a serum bilirubin of 3 mg. per 100 ml. or less. Neither liver nor spleen was enlarged. The moderately severe cases had a cord haemoglobin value greater than 11·2 g. but less than 14 g. per 100 ml. and the serum bilirubin was 3 mg. per 100 ml. or less. Some enlargement of liver and/or spleen was noted. The severe cases had a cord haemoglobin value of less than 11·2 g. and a serum bilirubin of more than 3 mg. per 100 ml., enlargement of liver and spleen, possibly bruising or oedema, and in one case a birth weight of less than $5\frac{1}{2}$ lb.

The aim of the operation was to employ 80-120 ml. of donor blood per lb. body weight, to use the umbilical route wherever possible and to effect the exchange fairly slowly.

There were cases where only a small volume was exchanged—for example, Case P. This infant was treated in another hospital. Attempts to employ the umbilical vein were unsuccessful and the registrar catheterized the long saphenous vein in the groin. Even here withdrawal was exceedingly difficult, and because the infant was only mildly affected the procedure was abandoned. In all cases the speed of exchange was fairly leisurely by intention, but in some it was prolonged by the technical difficulties encountered. The numbers are, of course, very small, but there is a reasonable distribution of severity. Five cases were mild, seven moderate and seven severe. If those cases which pursued a normal course are considered, four were mildly affected, three were of moderate severity and as many as five severe. Of the clinically abnormal cases, one was mildly affected, four were of moderate severity and only two severe. Of those showing the 'shock' picture, none had severe haemolytic disease. The only death occurred in the severely affected group. Only one other of this group (total seven cases) showed any abnormality, and this was limited to retching.

Regarding the speed of exchange, a total of 6·36 litres of blood was exchanged in the normal group in 1,386 minutes (excluding Cases K and P). The average rate of exchange was 4·6 ml. per minute. In the abnormal group a total of 4·12 litres of blood was exchanged in 968 minutes, so that the average speed of exchange was 4·3 ml. per minute. In the cases showing no clinical disturbance, therefore, the exchange was effected a shade more quickly on the average, but the fact that in the abnormal group intentional delays followed the occurrence of incidents, and so increased the duration of operation a little, must be kept in mind.

Pattern of Serum Electrolytes

Introductory Remarks. Analytical data referring to the cases investigated are charted in Figs. 1 and 2. Fig. 1 shows the individual results obtained from six normal transfusions, while Fig. 2 shows the individual results from seven transfusions at which clinical abnormalities were observed. From reference to the appropriate figures it will be apparent that they depict only the general trend of serum electrolytes during transfusion. It will be appreciated that, since specimens were collected at intervals during transfusion, it is only at these points that electrolytes could be assessed. Fluctuation must have occurred in the periods between collection of specimens, this fluctuation being influenced by movement of electrolytes in and out of the plasma compartment and, of course, by metabolic factors. Nevertheless, if this point be borne in mind in the evaluation of the results, it is believed that the general

pattern which emerges from this investigation adequately portrays the effect of infusion of citrated blood upon serum electrolytes.

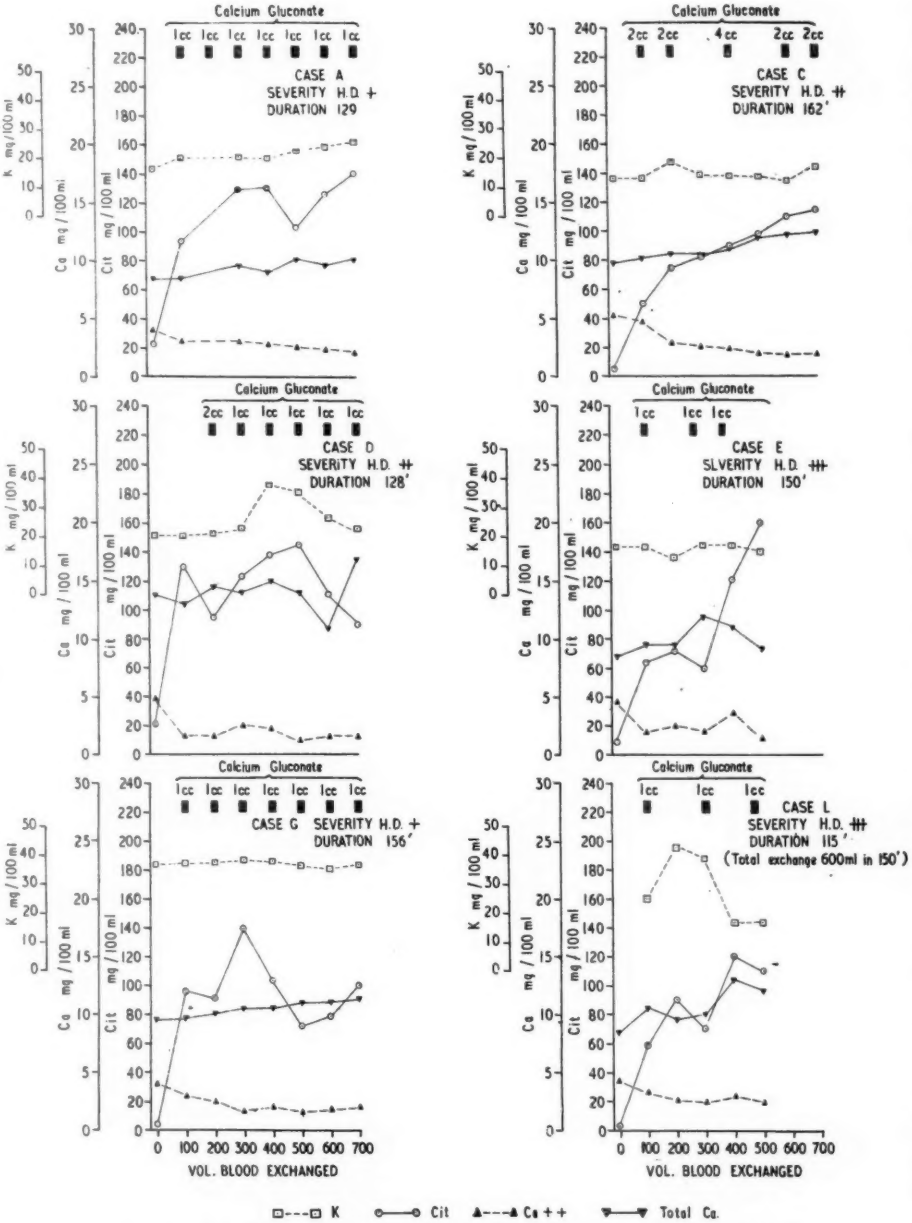

FIG. 1.—Serial serum electrolyte levels during six normal exchange transfusions.

The Group as a Whole. From the outset of the investigation attention was focused on the relationship of four biochemical situations to the clinical behaviour of the baby. These were: the influence of high citrate levels, of calcium-ion depression by citrate, of high serum potassium levels and the mutually reinforcing influences of a high potassium and a low calcium ion upon the heart. These are depicted in Figs. 3 and 4. In each graph every relevant analytical result in the series is included and marked by a symbol which denotes the clinical state of the patient at the time when the sample was taken. In Fig. 3 the coexisting citrate and calcium-ion levels are entered against each other. If high citrate levels *per se* were responsible for clinical abnormality, then the symbols denoting abnormal behaviour should be across the top of the graph. If clinical abnormality were the result of high citrate levels depressing calcium ion, however, then the abnormal cases should be at the top of the graph and towards the left. The upper part of the graph does not in fact contain the abnormal cases, nor do they lie predominantly to the left of the picture. The one death does lie in the top left-hand corner, but otherwise there is reasonable dispersal of the abnormal symbols among those which imply normal behaviour when the specimen was taken. In Fig. 4 the serum potassium levels were plotted against the coexisting levels of calcium ion. If hyperpotassaemia were responsible, then the abnormal cases

should lie across the top of the picture, whereas if depression of calcium ion were responsible, then they should lie to the left of the picture. If the offending biochemical upset were coexisting hyperpotassaemia and calcium-ion depression, then the abnormal cases should lie in the top left-hand quadrant. Apart from the important exception that the only death did in fact represent the highest serum potassium level at the lowest calcium-ion level, the other abnormal symbols are scattered across the

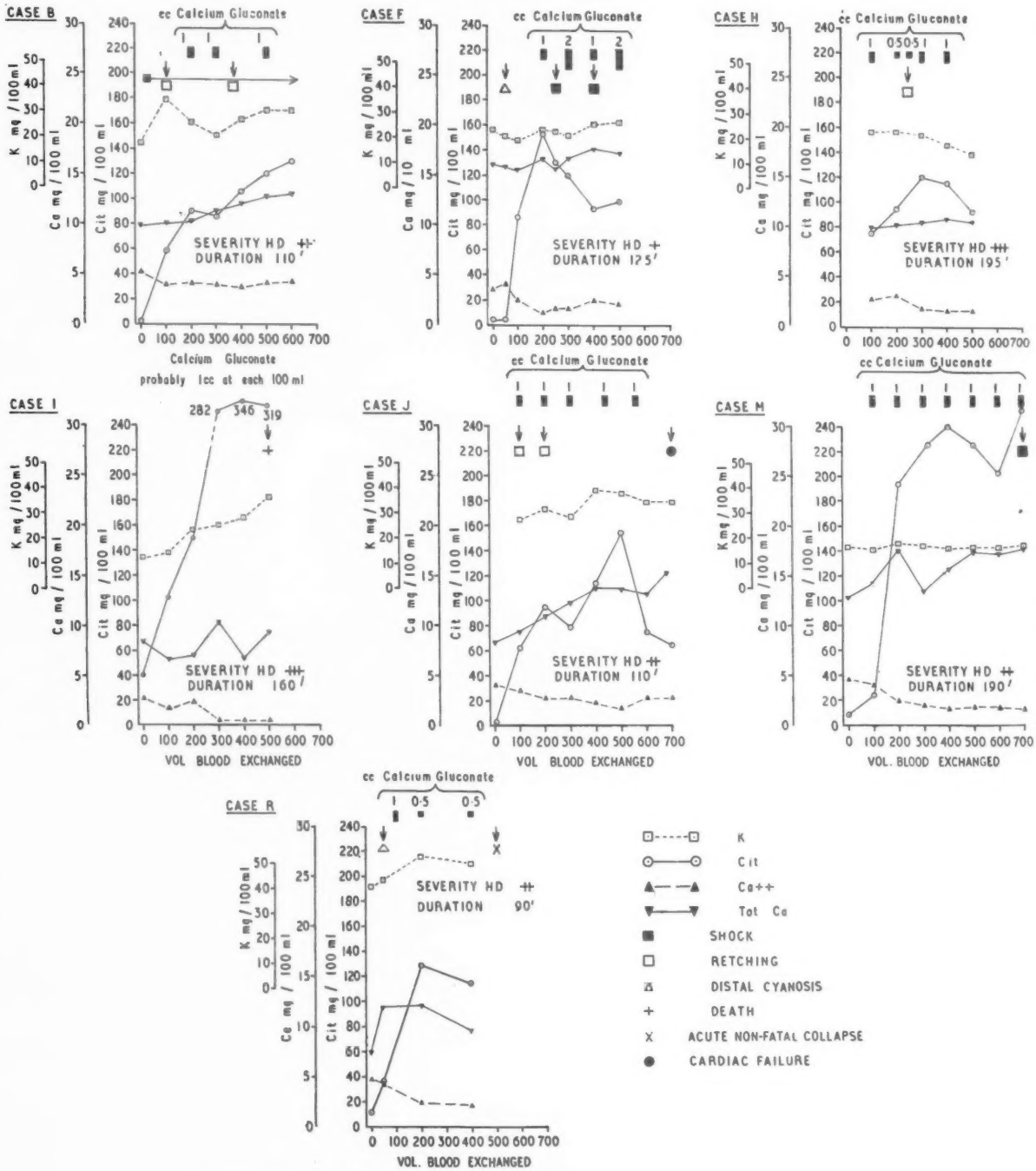

FIG. 2.—Serial serum electrolyte levels during seven abnormal exchange transfusions.

picture and fairly evenly disposed among the normal cases. From these two pictures it is possible to state that, with the exception of the fatal case, there was no relationship in this series of cases between the coexisting biochemical values and the clinical behaviour at the moment of taking the specimen.

It was apparent that a pattern of serum electrolytes during transfusion emerged from this investigation, this pattern being common to all infants whether or not clinical incident was observed. In summary, there appeared to be an increase in total calcium and citrate, a decrease in active calcium ion, and either no change or an increase in serum potassium. Several conclusions have been drawn from these results.

Citrate and Calcium. Great excess of citrate was found in the serum during exchange transfusion, and if, in fact, the formation of calcium citrate *in vivo* were dependent only upon chemical kinetic factors, then all available calcium ion in the plasma of these infants, except for the small amount liberated in the primary dissociation, should have been combined as calcium citrate. That this situation did not exist was apparent from the clinical state of the infants. The physiological environment, then, must be more complex than experiments *in vitro* would suggest, although all the calcium supplied in the form of calcium gluconate appeared to be inactivated immediately after injection (Fig. 5), if it can be presumed that calcium gluconate is completely ionized. The results are illustrated in Fig. 5. The absence of the classical manifestations of hypocalcaemia during transfusion even though subsequent analysis of serum showed a profound depression of calcium-ion concentration, is difficult

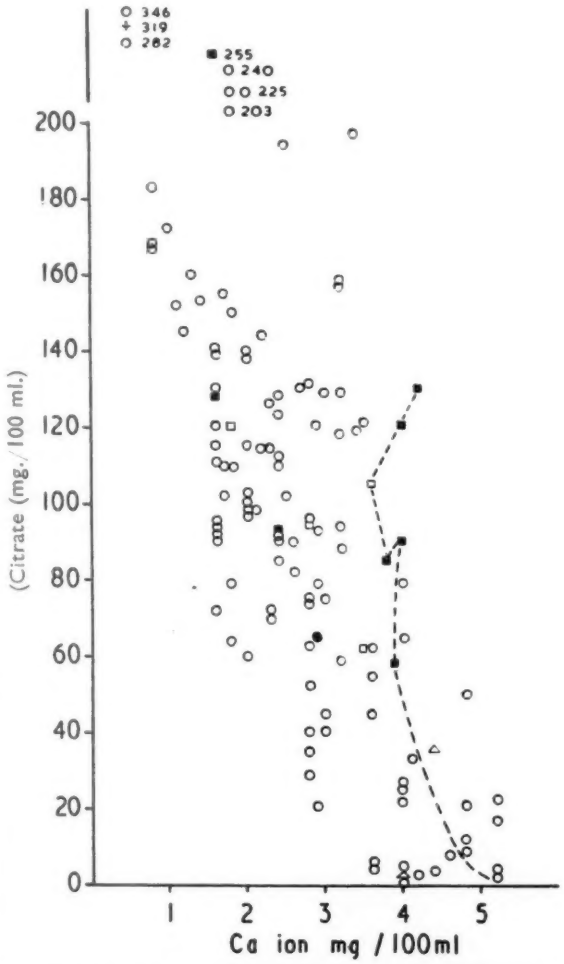

FIG. 3.—Clinical behaviour during exchange transfusion related to plasma values of citrate and calcium ion.

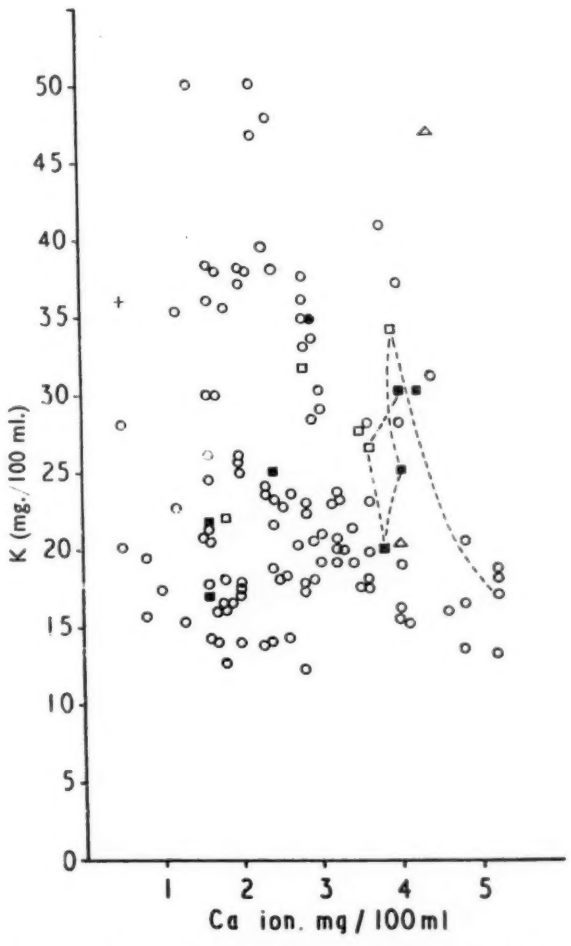

FIG. 4.—Clinical behaviour during exchange transfusion related to plasma values of potassium and calcium ion.

to explain. Since the formation of calcium citrate is known to be a slow reaction, it is suggested that complex formation may have been incomplete during transfusion, but on storage of the serum in the absence of active metabolic factors the reaction between citrate and calcium ions was able to reach completion.

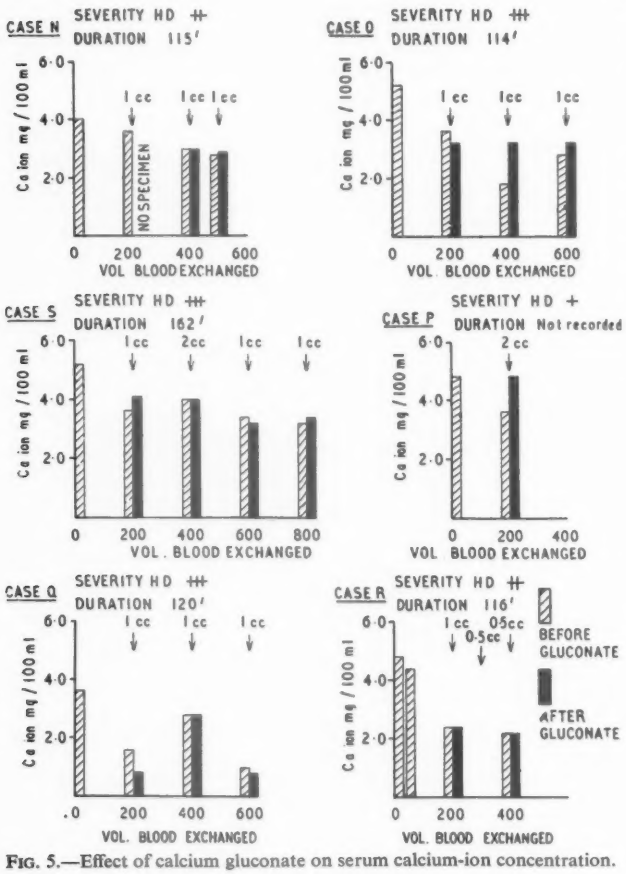

FIG. 5.—Effect of calcium gluconate on serum calcium-ion concentration.

It is claimed that during exchange transfusion the rate of transfusion is the most important factor in the development of hypercitraemia. Table I shows the infusion rate of citrate in this series, and it is apparent that the safety rate recommended by Mollison (1951) was commonly exceeded. There did not appear to be any correlation between the hypercitraemia and the citrate infusion rate, and it is considered significant that hypercitraemia of equal severity developed in both the clinically normal and abnormal groups. All infants showed considerable ability to 'metabolize' infused citrate, even in the presence of alleged hepatocellular immaturity.

It has been postulated that a high serum citrate level in the resting state is indicative of hepatocellular dysfunction. Hypercitraemia was commonly observed in the pre-transfusion state in this investigation. Natelson *et al.*, (1948) quoted the normal range of serum citrate as 1·5 to 6·0 mg. per 100 ml., with a mean value of 3·8 mg. per 100 ml., and in this series the range was 1·4 to 40·0 mg. per 100 ml., with a mean value of 12·6 mg. per 100 ml. The fatal case had a resting serum citrate level of 40·0 mg. per 100 ml., yet post-mortem examination revealed no gross hepatocellular damage. Furthermore, liver enlargement was not a common feature in any of the other cases, but this does not exclude the possibility of a 'metabolic' immaturity existing. Confirmatory evidence of high resting citrate values has been provided by the low level of resting serum calcium ion observed in this series.

TABLE 1

TABLE RELATING RATE OF TRANSFUSION, RATE OF CITRATE INFUSION AND INCIDENCE OF CLINICAL ABNORMALITY

Case	Severity of Haemolytic Disease	Birth Weight (kg.)	Volume of Blood Exchanged (ml.)	Time taken for Exchange (minutes)	Citrate Infused (mg./kg./hr.)	Incident
A	+	3·2	700	129	286	—
B	++	2·9	600	107	397	Shock, retching
C	++	3·3	700	162	202	—
D	++	3·2	700	128	400	—
E	+++	2·5	500	150	356	—
F	+	2·6	500	125	—	Distal cyanosis
G	+	3·5	700	156	293	—
H	+++	2·3	500	195	242	Retching
I	+++	2·7	500	160	218	Death
J	++	3·3	850	110	542	Retching, heart failure
K	+	3·2	300	240	80	—
L	+++	3·0	600	150	385	—
M	++	2·7	700	190	240	Shock
N	++	2·6	500	115	404	—
O	+++	3·8	600	114	302	—
P	+	—	200	Not recorded	—	—
Q	+++	3·2	560	120	303	—
R	++	3·6	470	81	298	Distal cyanosis, acute collapse
S	+++	3·8	800	162	334	—

Potassium. Variations in serum potassium during exchange transfusion were unpredictable. Hill (1954) quoted the normal range of serum potassium in the newborn infant as 17·5 to 21·1 mg. per 100 ml. In this series the normal pre-transfusion range was 13·3 to 40·0 mg. per 100 ml. Table 3 shows that five infants (F, G, K, N, R) had pre-transfusion serum potassium levels above normal, and in these instances either no change or a rise accompanied the transfusion. Of those infants who had a normal pre-transfusion serum potassium level, five (B, D, I, J, L) developed a hyperpotassaemia during transfusion. All these infants were transfused with donor blood with a plasma potassium content of over 30·0 mg. per 100 ml. Except in the fatal case, however, the hyperpotassaemia was not relatable to any particular clinical abnormality, since the phenomenon was observed in both clinically normal and abnormal infants. Furthermore, two infants classified as clinically abnormal (H, M) had a normal serum potassium level throughout transfusion. One point is worthy of note: the plasma potassium level of the donor blood used in the fatal case was 110 mg. per 100 ml., and at death coexisting high potassium and low calcium-ion concentrations were recorded. Whether the high potassium level influenced the onset of cardiac failure could not be ascertained, since electrolyte imbalance was not considered to be the cause of death.

TABLE 2
ANALYSIS OF CASES ACCORDING TO SEVERITY OF HAEMOLYTIC DISEASE

	+	++	+++
Total number of cases	5	7	7
Clinically normal	4	3	5
Clinically abnormal	1	4	2
(*a*) Shocked	1	2	—
(*b*) Retching	—	2	1
(*c*) In cardiac failure	—	1	—
(*d*) Acutely collapsed	—	1	—
(*e*) Dead	—	—	1

Summary of Biochemical Changes in Abnormal Cases

Fig. 2 illustrates serum electrolyte changes during exchange transfusion in the abnormal cases.

Distal Cyanosis. This was not associated with any particular electrolyte pattern. Symptoms appeared early in the exchange, and at a time when serum citrate was beginning to rise and serum-calcium ion to fall. Both infants had a pre-transfusion hyperpotassaemia, which persisted throughout transfusion.

Retching (Cases B, H, J). This was associated with a hyperpotassaemia, a rising serum citrate level, and a serum calcium ion which was by no means unduly low when compared with other apparently normal transfusions.

Shock (Cases B, F, M). In Case B, shock appeared before any marked change in either serum citrate or calcium ion, but hyperpotassaemia was present after only 100 ml. of blood had been exchanged, and therefore coexisted with the appearance of clinical signs of shock. Case F presented

TABLE 3
CHANGES IN SERUM POTASSIUM DURING EXCHANGE TRANSFUSION

Case	Volume of Blood Exchanged (ml.)							
	0	100	200	300	400	500	600	700
	Serum Potassium (mg. per 100 ml.)							
A	16·2	20·5	—	20·8	20·4	22·7	24·0	25·7
B	17·0	34·0	25·0	20·0	26·5	30·0	30·0	—
C	13·3	13·6	19·0	14·3	14·0	14·0	12·7	17·7
D	20·5	20·5	21·4	23·2	38·0	35·4	26·0	24·4
E	16·1	16·1	13·8	17·4	17·5	15·4	—	—
F	23·1	18·8	22·7	20·6	25·1	26·0	—	—
G	37·0	37·5	38·0	38·4	38·2	36·2	35·7	37·0
H	—	23·0	23·1	22·0	17·8	14·4	—	—
I	12·4	14·0	18·0	20·0	28·0	36·0	—	—
J	—	27·7	31·6	28·3	39·5	38·0	34·8	34·8
K	31·0	36·0	30·0	50·0	—	—	—	—
L	—	20·0	24·5	23·5	18·0	18·0	—	—
M	16·5	15·7	18·2	17·0	16·0	16·5	16·5	17·1
N	28·0	—	28·0	—	29·0	—	33·0	—
O	18·7	—	18·1	—	21·7	—	22·4	—
P	17·7	—	24·3	—	—	—	—	—
Q	19·9	—	21·8	—	17·8	—	17·3	—
R	40·8	—	53·2	—	50·1	—	—	—
S	18·0	—	17·6	—	24·8	—	21·4	19·0
Mean value	21·6	22·9	24·9	24·3	26·0	25·2	26·7	25·0

only a mild hyperpotassaemia. Signs of shock appeared towards the end of the transfusion in Case M. At this time the serum citrate level had suddenly increased to 250 mg. per 100 ml., but serum potassium was within the normal range. Serum calcium-ion level was apparently uninfluenced by the sudden change in citrate, remaining, as it had done throughout the transfusion, at about 2 mg. per 100 ml.

Cardiac Failure (Case J). Heart failure appeared at a point in the transfusion when the serum electrolytes were beginning to return towards normal. The citrate level had fallen substantially, total calcium had reached a peak of 15 mg. per 100 ml., calcium ion had risen by 1·0 mg. per 100 ml., and serum potassium had fallen by 5 mg. per 100 ml. to a level of 30 mg. per 100 ml.

Acute Non-fatal Collapse (Case R). The infant collapsed after 500 ml. of blood had been exchanged, and the nearest sample of blood to this incident, taken at 400 ml., indicated a profound hyperpotassaemia although the serum citrate level was falling and the serum calcium ion was relatively stable at 2 mg. per 100 ml. It is significant that the bottle of donor blood had been changed after 400 ml. had been transfused, and the plasma potassium concentrations in the two bottles were 85·4 mg. and 52·8 mg. per 100 ml. respectively. The plasma potassium value after the exchange of 400 ml. of blood, although high, was actually a little lower than it had been earlier, and a further reduction might have been expected by the time of the clinical incident, in view of the lower plasma potassium content of the second bottle.

Death (Case I). In the fatal case, serum citrate had reached by far the highest level in the series, yet death took place when the citrate level was beginning to decrease. Serum calcium-ion concentration was not measurable, nor had it been for some time before death. At the time of death serum potassium had reached a peak value of 36 mg. per 100 ml. Thus there existed a profound hypocalcaemia and hyperpotassaemia.

Hyperpotassaemia. This was the only constant feature of the abnormal cases, and it was severe in the cases of cardiac failure, acute non-fatal collapse and death. Three apparently normal infants (D, G, L), however, exhibited hyperpotassaemia of similar magnitude.

Conclusion. It is believed that none of the clinical incidents was due entirely to electrolytic imbalance, since similar biochemical changes were common to all the infants of the series. Serum electrolytes reflect the total electrolyte pattern to some degree, but clinical abnormality need not necessarily be the result of a sudden change in plasma electrolytes. Rather it may be due to prolonged exposure of the intracellular environment to a gradually changing extracellular environment. Considered from this point of view, a study of serum electrolytes throughout a transfusion is more important than the assessment of electrolytes at any particular instant in a transfusion. Critical evaluation of the results of this investigation has failed to show a correlation between electrolytic imbalance and clinical abnormality during transfusion, but there is no doubt that all infants undergoing exchange transfusion are exposed to an abnormal biochemical state over a prolonged period.

GENERAL DISCUSSION

Citrate

Hypercitraemia. The possible importance of rising levels of plasma citrate in the production of symptoms during infusion of citrated blood was emphasized by Wexler *et al.* (1949) and Ames *et al.* (1950). The level of citrate was found to rise to a figure 10 to 30 times greater than the pre-transfusion value. This was accompanied by a decrease in plasma calcium-ion concentration. Prolongation of the Q-T interval on ECG tracings was recorded by Ames *et al.* (1950). Although the latter could be attributed to the depression of calcium-ion concentration by citrate, no constant relationship existed between the plasma citrate concentration and the ECG change. Furthermore, the Q-T interval could return to normal in the presence of continued high levels of citrate. These studies were made on convalescent infants. Plasma citrate, total calcium and total protein were determined, and plasma calcium-ion concentration was assessed indirectly by employing the normogram of McLean and Hastings (1935). Several of the babies became irritable during the infusion; their skins were pale and mottled, and a normal skin temperature was not restored by the use of blankets alone. One infant collapsed suddenly and responded only to prolonged resuscitative measures. Another was found dead during transfusion. The authors considered that these acute disturbances were almost certainly the result of acute lowering of plasma calcium-ion level. Critical study of the case records, however, shows no convincing evidence for such a belief and reveals the presence of other factors predisposing to complication. They believed that the absence of reactions

in the majority of cases might be explained on the basis of the existence of forces capable of counteracting the calcium-ion-lowering effect of citrate. However, they provide no explanation of why these two less fortunate individuals should have been deficient in this homoeostatic mechanism. More recently Bunker *et al.* (1955) have shown, in a series of 130 adults who received moderate to large volumes of citrated blood, that many patients developed hypercitraemia, and theoretically calcium-ion concentration in the plasma ought to have been seriously depressed. More marked elevation of plasma citrate occurred when transfusion was extremely rapid, prolonged or repeated. Higher levels also occurred where the liver was damaged, and this may be important in the newborn infant with or without haemolytic disease.

The present investigation has demonstrated conclusively that a great increase in serum citrate occurs during the infusion of citrated blood, and it is important to consider the facts which influence this phenomenon. The acid-citrate-dextrose mixture used as an anticoagulant in this country has been criticized and praised for many years. When it was first instituted the dangers of citrate were emphasized, but until the technique of replacement transfusion and massive blood transfusion became common, little attention was focused upon the possibility of citrate intoxication in medical practice. In the infants in this series, amounts of citrate ranging from 738 to 3,413 mg. were infused into a plasma compartment of less than 200 ml. average volume, so that accumulation of citrate under these circumstances could be dangerous. It is believed that citrate in stored donor blood is confined essentially to the plasma. Thus, if the recommended ratio of volume of anticoagulant to blood is strictly adhered to, then the plasma citrate content of the donor blood should be about 600 mg. per 100 ml. It will be appreciated that any marked deviation from the standard technique may result in significant changes in the plasma citrate. Ames particularly emphasized this point when describing an alleged case of citrate intoxication following the infusion of plasma containing 1,536 mg. of citrate per 100 ml. With this in mind Walker and Neligan (1955) recommend the use of packed cells in exchange transfusion.

Speed of Citrate Infusion. Although the plasma citrate level in the donor blood is the first consideration, the rate at which it is infused is obviously important. It is desirable that the rate of transfusion be adjusted so that the homoeostatic mechanisms controlling citrate are able to deal with the citrate as fast as it is being infused. Mollison (1956) stipulates a maximum rate of 260 mg. of citrate per kg. of body weight per hour, but Wexler *et al.* (1949) and Walker *et al.* (1955) freely admit to exceeding this rate without clinical incident. In the present series similar conditions prevailed. Nakasone *et al.* (1954) performed an interesting experiment in which citrate solutions of varying strengths were infused into dogs and the response of cardiac muscle was measured by ECG tracings. They suggested that it was not the actual level of citrate in the perfusate which was the factor precipitating cardiac changes, but rather the cumulative dose of citrate in the animal's body. In other words, hypocalcaemia was induced after the infusion of a critical amount of citrate, whether this was attained over a short period by the infusion of a solution containing a high concentration of citrate or after a longer period with a solution containing less citrate. For this reason the slower the rate of transfusion the less severe the hypercitraemia which will develop. It is suggested that the clinical incidents in this series were not related to the infusion rate of citrate. Reference to Table 1 will show that the safety rate was often exceeded in cases which appeared normal throughout transfusion, yet in other abnormal cases the infusion rate was below the recommended safety rate.

Metabolism of Citrate. It should be borne in mind that reports describing rapid metabolic breakdown of citrate during the infusion of citrated blood are based on observations of plasma citrate concentration during a period when rapid diffusion out of the plasma compartment is occurring. Transfer of citrate to other compartments of body water would account, at least in part, for the disappearance of exogenous citrate out of the plasma water. The average amount of citrate contained in 100 ml. of citrated donor blood is 370 mg. Assuming that no transfer occurred out of the plasma compartment into interstitial water, then the amount of this citrate which would be retained after the exchange of 100 ml. of blood by the technique employed in this investigation would be about 320 mg. In practice, however, a proportion of this would be transferred to interstitial water, and, assuming even distribution throughout the extracellular water, about a seven-fold reduction in the theoretical maximum plasma concentration could be expected. The actual level in the plasma would depend on the degree of transfer of the citrate at the time of collection of the specimen, but it should be within the range of 46-320 mg. per 100 ml. Thus the levels recorded in this series indicate that a considerable portion of infused citrate migrated

out of the plasma compartment after each 100 ml. of blood exchanged. Increased intracellular metabolism of citrate was likely to occur under the stimulus of the infusion of citrate. The exact rate of oxidation of citrate in the human being is unknown, but toxic effects appear to depend on dosage and rate of administration. Most tissues contain a specified citric-acid dehydrogenase, the liver and renal parenchyma being the most active sites of metabolism (Thunberg, 1953; Mårtensson, 1940). Wexler observed delayed removal of citrate from plasma in one fatal case which showed gross liver damage at necropsy, and from this evidence he postulated that delayed citrate metabolism might result from impaired liver function. In the fatal case of the present series a similar delayed removal of citrate was observed, yet post-mortem examination revealed no severe liver damage. It is quite possible that a mild degree of metabolic immaturity exists in newborn infants, especially those suffering from erythroblastosis foetalis. This would explain the resting hypercitraemia observed in some cases in this series. It can only be concluded, however, that all infants appeared to have efficient homoeostatic mechanisms for removing infused citrate from plasma.

It is suggested as a hypothesis that all the factors discussed must operate during the infusion of citrated blood. Initially the prevention of severe hypercitraemia by careful adjustment of the donor plasma citrate level and the rate of transfusion can be controlled by the operator. Presumably any infused citrate enters the plasma, and from there it is transferred to interstitial water and finally to the intracellular water, where it is metabolized. Reference to Figs. 1 and 2 will indicate the general pattern of serum citrate during transfusion. The initial dramatic rise to a level between 100 and 160 mg. per 100 ml. may represent a phase in which citrate is essentially confined to the plasma. Once mechanisms controlling transfer out of the plasma compartment become operative it is reasonable to expect a fall in the plasma citrate if the rate of transfer exceeds the rate of citrate infusion in the plasma. This has been confirmed in the present investigation. Fluctuations observed at later stages in the transfusion may reflect the efficiency of intracellular metabolic pathways. Thus a rising citrate in the presence of a constant rate of citrate infusion suggests some impairment of function (Cases I, M). Conversely, a falling serum citrate level suggests efficient metabolism, while a fluctuating citrate level may be indicative of sudden changes in the citrate intake with which the intracellular metabolic processes are unable to cope. All except two infants (I, M) were able to metabolize infused citrate very efficiently. If citrate intoxication were the causative factor in some or all of the clinical incidents in this series, then it is difficult to explain the fact that serum citrate levels of a similar magnitude did not precipitate incidents in the normal infants.

Citrate-induced Hypocalcaemia. The high serum citrate recorded in this investigation should have induced severe hypocalcaemia. The theoretical implications are that all available calcium ions in the plasma of infants undergoing transfusion should be inactivated, but the results indicate that, although significantly reduced, this reduction was not complete except in the fatal case. Two explanations are proposed. First, citrate was present in the plasma in high concentration, but there was no evidence to show whether the whole or part of it was present in an active ionic form. In fact an inactive molecule, possibly bound to protein, may have existed. Such complexes are known to exist in the case of protein and glucose and the lipoproteins. Under such circumstances only ionized citrate would be available for reaction with calcium and other cations. Secondly, the formation of calcium citrate is not an instantaneous reaction, and this might explain the apparent discrepancy between the absence of clinical manifestations of tetany, even though subsequent analysis of serum showed a profound depression of calcium ion. During transfusion calcium citrate formation may have been incomplete, whereas on storage of the serum in the absence of enzyme action, reaction was allowed to reach completion in the presence of excess of citrate ion. Whatever the explanation, analysis revealed that complete inactivation of calcium ion in serum did not occur. There was no evidence to confirm the finding of others (Lansing and Scott, 1942) that significant mobilization of calcium ion occurred from intracellular sources, nor did it appear that the injection of calcium gluconate was effective in elevating calcium ion in serum. On clinical grounds, Walker and Neligan (1955) abandoned the use of gluconate, and they did not observe tetany in a series of 272 transfusions.

Herlitz (1942) observed active tetany in infants whose plasma calcium-ion level had fallen below 3·5 mg. per 100 ml., yet even with serum calcium-ion levels below 2·0 mg. per 100 ml., classical tetany was not seen during this investigation. The absence of clinical abnormality is not inconsistent with a reduction in calcium ion, as the factors governing neuromuscular irritability are complex, and the maintenance of a normal state of irritability may

have been due to compensatory mechanisms. The exact means by which tetany is brought about has not yet been elucidated, but the original work of Ringer and Loeb (discussed in any standard textbook of physiology) might elucidate the problem. They postulated a delicate equilibrium between the cations of the serum, and any disturbance of this equilibrium, such as a decrease in calcium, magnesium or hydrogen ions or an increase in sodium, potassium or hydroxyl ions, causes hyperirritability of the tissues. It has been shown in this series that an increase in potassium and a decrease in calcium ion occurred in serum, thus favouring the development of neuromuscular hyperirritability.

It has been demonstrated that citrated blood is weakly acid in reaction, and the infusion of such a medium would favour the production of a metabolic acidosis. This problem is at present under investigation by Walker (personal communication, 1956), but no results have been reported to date. Increase in hydrogen-ion concentration would tend to compensate for the coexisting hypocalcaemia and hyperpotassaemia in terms of neuromuscular irritability. For example, Mudge and Vislocky (1949) observed that the acidosis of chronic renal disease was not specifically related to a change in acid-base equilibrium, but was associated with a decrease in intracellular potassium and a rise in intracellular sodium. In this investigation perfusion of donor blood did not significantly alter the infants' sodium level in the face of a virtual replacement of their blood and a donor plasma concentration around 400 mg. per 100 ml. Since renal excretion of sodium must have been negligible during transfusion, diffusion or transfer of excess sodium out of the plasma compartment must have occurred. Is it reasonable to postulate that at least some of this sodium entered the intracellular water, possibly reflecting that some movement of potassium into the extracellular water had occurred?

Potassium

The leakage of potassium from red blood cells during storage is a well-known phenomenon (De Gowin *et al.*, 1940), and the significance of this was emphasized by Mollison (1951). Toxic levels of potassium in blood plasma are associated with cardiac arrest, and in fact the injection of potassium citrate solution into the coronary circulation has been used experimentally to produce elective temporary cardiac arrest (Melrose *et al.*, 1955). In the adult the transfusion of one or two pints of blood does not greatly affect the recipient's plasma potassium concentration, but the situation is different during exchange transfusion in a newborn infant, where one pint of blood is equivalent to about twice the infant's blood volume. The influence of transfusion upon serum potassium concentration in eight infants was studied by Miller *et al.* (1954). Hyperpotassaemia was present, particularly when the donor blood had been stored for a week or longer. No convincing proof was offered that the high potassium levels were harmful to these infants. Sudden unexplained death in two infants also prompted the investigation carried out by Campbell (1955). Hyperpotassaemia was present in three of four deaths in the series, but comparably high figures were recorded in infants who had shown no abnormality. Although the levels were potentially lethal, Campbell was unable to ascribe the deaths with certainty to hyperpotassaemia. Some success was obtained with insulin in maintaining more normal potassium levels, and the author's experience of comparative morbidity and mortality in comparable control and test groups is awaited with interest.

Serum potassium levels recorded in the present investigation indicated that 60% of infants developed a hyperpotassaemia either before or during transfusion, but these changes were common, even in the asymptomatic infants. Rise in plasma potassium level during exchange transfusion is influenced by the intake of potassium in the donor plasma, the ability of the renal mechanism to excrete excess potassium and the efficiency of intracellular 'metabolic' sites in removing potassium from the plasma. It was apparent in this investigation that the development of hyperpotassaemia was closely related to the infusion of donor blood. The incidence of hyperpotassaemia was high when the donor plasma potassium level exceeded 30·0 mg. per 100 ml. As in the case of citrate, however, the high serum potassium levels were not relatable, surprisingly, to the rate of transfusion. Thus the development of hyperpotassaemia may be due to accumulation of potassium rather than to the potassium concentration of the perfusate. In the adult renal excretion of potassium is a most important homoeostatic mechanism preventing potassium intoxication, but, since renal immaturity is an accepted phenomenon in the newborn, their ability to excrete excess potassium is doubtful. In fact the mean normal urine output in the first 24 hours is about 20 ml., so that the maintenance of a normal serum level during transfusion must depend upon mechanisms other than renal. One of these must be the transfer of potassium from the plasma to other compartments of the body water. Simple distribution within the extracellular water will result in a seven-fold decrease in the concentration of any exogenous potassium which is confined initially to the plasma. The serum potassium

concentration *per se* does not necessarily reflect the state of cellular potassium, and it is not justifiable automatically to associate a high serum potassium level with a toxic accumulation of potassium in body water. In fact Tarail and Elkinton (1949) have shown that a cellular deficiency of potassium may exist in the presence of a high serum potassium level. Although this would explain the absence of potassium intoxication in the cases in this investigation with a high serum potassium level, it is difficult to imagine in infants suffering from erythroblastosis foetalis. These infants are exposed to a severe haemolytic process which starts *in utero*, and it is possible that in the absence of a renal homoeostatic mechanism these infants are in a state of positive potassium balance. This fact tends to be confirmed by the high incidence of resting hyperpotassaemia.

Experiments (Joseph *et al.*, 1939; Fenn, 1939; Houssay *et al.*, 1936; Eichelberger, 1941) have shown that the intravenous injection of soluble potassium salts results in the accumulation of potassium within the liver cells, and this process is enhanced by the simultaneous infusion of glucose solution. Presumably potassium enters the intracellular space of the hepatic cells during hepatic glycogenesis. This is suggested as a working hypothesis in the present investigation. The liver is only a temporary site, but it serves as a means of preventing potassium intoxication in the absence of renal regulating mechanisms. The liberation of potassium during glycogenolysis inevitably occurs, but at a rate which allows adequate renal excretion of potassium by the maturing renal tissue.

Coexistent Hypocalcaemia and Hyperpotassaemia

The biochemical abnormality observed in this investigation was the coexisting hyperpotassaemia and hypocalcaemia. The danger of simultaneously rising potassium and falling calcium-ion levels in the blood was described by Guest (1952). Protection of dogs against normally lethal concentrations of potassium may be provided by the intravenous injection of calcium (Winkler *et al.*, 1939). Modification of the effects of potassium intoxication in children by the administration of calcium salts was claimed by Govan and Weiseth (1946). Latent tetany in a group of adults with coexisting hypopotassaemia and hypocalcaemia was rendered manifest by the slow intravenous infusion of potassium salts even though the final plasma potassium level did not exceed the usual normal range (Engel *et al.*, 1949). More recently Levine *et al.* (1952) have claimed that hypocalcaemia may actually potentiate the electrocardiographic signs of hyperpotassaemia. None of these facts was confirmed in this investigation. There is some suggestion that the hyperpotassaemia may have precipitated heart signs in the cases of acute non-fatal collapse, cardiac failure and death, but completely asymptomatic infants presented a hyperpotassaemia of similar magnitude. The evidence is strong in favour of profound electrolytic imbalance in the fatal case, although the actual cause of death was found to be haemorrhage. It appears that there is no association between the clinical disturbance observed during exchange transfusion and the changes which undoubtedly occur in plasma electrolytes.

Other Possible Explanations of the Clinical Disturbances

Circulatory Stress

Interference with Postnatal Readjustment of Circulation. The picture of differential cyanosis of the distal half of the body is most alarming. Only two such cases have been seen by J. W. F. and both occurred in this series. In each great difficulty had been met in withdrawing blood and much time had been spent manipulating the catheter. On the first occasion the development of some venacaval obstruction was considered, and the spontaneous resolution of the disturbance was witnessed with relief. The production of a temporary veno-arterial shunt through a patent ductus arteriosus must be considered. Increasing experimental evidence is becoming available that the ductus arteriosus does not close within a few minutes after birth. The careful studies of lambs by Dawes *et al.* (1954) and Born *et al.* (1956) at Oxford have shown that in that animal the closure takes place over hours, and is dependent on changes in oxygen tension and the release of sympathetic amines.

The occasional observation of cyanosis of the lower part of the body of newly born babies stimulated Eldridge *et al.* (1954) to carry out oxygen saturation studies upon arterialized capillary blood from the right hand and foot of healthy newborn human infants; 14 studies were made on 12 subjects. Of the 14 studies, eight showed significantly lower values in the foot than in the hand. In all five studied from one to three hours after delivery the oxygen saturation of blood from the foot was significantly lower than in the hand, indicating the presence of a veno-arterial shunt to the lower part of the body. Three of the five infants studied from three hours to three days after birth showed lower blood oxygen-saturation values in the foot than in the hand. None of the four infants who were older than three days showed significant oxygen-saturation differences. One baby who had a significant

difference at two hours which persisted at two days showed no difference between hand and foot values by the fifth day. Should these studies be confirmed, then exchange transfusion is being carried out at a time when the ductus may be open functionally and when it may be the site of a veno-arterial shunt.

From this it is but a step to the fact that the increase in pressure in the right side of the heart which may occur during exchange transfusion may increase the right-to-left shunt through the ductus and give rise to visible cyanosis in the distal half of the body. The increased pressure might be the result of a weakened myocardium going into failure, of excessively rapid transfusion or of partial spasm of the great abdominal veins which would act normally as a blood reservoir. Such an explanation is not entirely satisfactory, however. If the cyanosis were the result of a veno-arterial shunt through the ductus, it is surprising that it appeared in the very early stages of operation, that it did not become progressively more noticeable and that it resolved although operation was continued. Perhaps the withdrawal of the catheter for a few centimetres was responsible, as the blood flow which had been directed through the ductus venosus to the vena cava close to the heart would then be subjected to the cushioning effect of the portal circulation. Even if this were so, a major difficulty still remains. There was no doubt that the superficial veins over the front of the abdomen became much more obvious and that they drained upward over the chest. They did not constitute convincing evidence of occlusion of the inferior vena cava, but they suggested it. Catheterization of the umbilical vein takes the catheter tip to the inferior vena cava at 12-14 cm. from the abdominal wall (van Loghem *et al.*, 1949). When obstruction is encountered at 10-11 cm., the catheter may have turned into the portal circulation and the withdrawal of blood may be very difficult or even impossible. Catheterization of the ductus venosus is not easy, but from a knowledge of the length of polythene tube introduced into these two infants the catheter tips must have lain in the ductus venosus or in the portal circulation. 'The fact that veins are capable of constriction may be observed by anyone who attempts to insert a cannula into one without due care' (McDowall, 1938). The ductus venosus is a foetal vessel which is in process of establishing or maintaining functional closure at the time when an exchange transfusion is being carried out. Irritation by a catheter could be expected to intensify the muscular constriction. The vessel is relatively short and it enters the inferior vena cava.

As a possible explanation for a very curious phenomenon it is suggested that spasm spreading to the greater vessel and producing partial occlusion merits consideration. Resolution of the physical signs might then follow partial withdrawal of the catheter and relaxation of the vena cava. Sphincter mechanisms exist on the great veins of some mammals. The dog has one on the hepatic vein, and the common seal has one on the posterior inferior vena cava (Harrison and Tomlinson, 1956). No reference can be found to the existence of any such structure in the human embryo at any point in development. Spasm of the inferior vena cava of animals may occur, however, as a reflex phenomenon in the absence of any recognizable sphincter. The fact that the vena cava of the horse could be made to constrict by stimulating the abdominal sympathetic was recorded by Valentin (1839). Splanchnic stimulation can cause constriction of the inferior vena cava (McDowall, 1938), and the portal vein can be made to constrict similarly (Burton-Opitz, 1913). Furthermore, Neil (quoted by McDowall, 1956) has obtained records of post-ganglionic sympathetic activity in fibres supplying the superior and inferior venae cavae. Such impulse discharge is markedly increased reflexly by such a remote procedure as the perfusion of the carotid-body areas with blood of low oxygen saturation. With spasm of the vena cava in mind, radiological studies employing a contrast medium were planned for such further cases as might be encountered, but none has occurred.

Even if both these explanations should be incorrect, the phenomenon, of which there may be milder unobserved degrees, reminds the paediatrician that he is producing acute dynamic changes in a circulatory system which is undergoing simultaneous adaptation to extra-uterine life. Following the occurrence of the second case the catheter tip has never been inserted for more than 7-8 cm. from the abdominal wall. The employment of less rigid catheter material may have some advantage (Tizard, 1957).

Speed of Exchange. The development of signs of cardiac failure during exchange transfusion is not uncommon, but, apart from the unknown importance of the coexisting hyperpotassaemia and reduced calcium ion in Case I, the other biochemical findings in the series were unassociated with cardiac failure. The mechanical stress of exchange transfusion must be considerable. When a 7 lb. baby receives an 80 ml. per lb. body weight exchange he is subjected to a constant withdrawal and replacement of from 3% to 7% of his blood volume every

two to three minutes for 1½ to 2 hours. This takes place in a subject whose myocardium may be unhealthy before operation is begun and who may have other weak points in the circulatory system. The spleen, for example, may rupture either spontaneously or during exchange transfusion. In 1949 an exchange transfusion by the umbilical route was carried out by one of us (J. W. F.) on a severely affected baby of 5 lb. weight. Twenty-ml. aliquots of blood were used and all seemed well until 380 ml. had been exchanged. The infant then collapsed suddenly and died in a few moments. The catheter was clamped *in situ*, and at necropsy its tip was found in the inferior vena cava near the right atrium. The right side of the heart was extremely dilated. No other abnormality was found and the death may be attributed to the author's inexperience.

The deterioration observed so commonly by Walker and Neligan (1955) was thought to be unrelated to the initial condition of the infants, the birth weight, technical difficulties encountered or the rate of exchange. Yet at least one of their subjects was so delicately balanced that the injection of only 10 ml. at one point in an exchange transfusion dramatically converted an apparently well baby into a dead one. The effect of the too-rapid transfusion of anaemic patients was described by Starling (1918) as being like an overloaded heart-lung preparation. Venous pressure rises and cardiac output falls. Referring to what Wiener (1943) has described as 'speed shock', the *British Medical Journal* (1955) points out that the circulatory collapse is related, not to the properties of the stored blood, but to the total volume given and the speed of administration. The ability of children to tolerate relatively faster transfusion than adults was mentioned by Andrews and Coleman (1957), but their subjects were aged 4 years or more.

The need for care and experience in carrying out exchange transfusion has been stressed by Philipsborn *et al.* (1956). They found from the literature that most exchange transfusions were carried out in from one to two hours, and decided to investigate the effect of rapid exchange transfusion in pups. The operation was carried out on healthy mongrel pups through the femoral artery and employing their own heparinized blood. They discovered that much larger aliquots of blood could be used with safety than had been anticipated, and that the vascular trees of puppies could be expanded or contracted by as much as 25% without significantly altering the venous or arterial pressures or provoking changes in the ECG.

Circulatory equilibrium could be maintained under challenges far exceeding those which ordinarily occur during exchange transfusion. When two of the puppies were subjected to additional stress (barbiturate overdosage in one and exsanguination shock in another), however, they were less able to face the challenge of rapid exchange transfusion. There are obvious differences between the animal experiment and the human operation. The experiment employed healthy puppies receiving their own warm heparinized blood by the femoral artery, whereas the operation is carried out on human infants who have been the victims of a pathological process for some weeks and possibly involving the circulatory system, and who receive cool or cold stored citrated blood by the portal circulation.

Whatever the part played by excessive speed in the production of symptoms during exchange transfusion, the surgical principle of gentleness in operating is likely to be less upsetting to an infant than haste and undue manipulation. Where signs of distress appear they frequently subside if the baby is left undisturbed for five or ten minutes, and if cardiac failure is definitely present a small venesection may be carried out with advantage. Clinical deterioration may take place, however, in the absence of the classical signs of cardiac failure. The descriptive term 'shock' has been applied here to those infants who become cold, pale and limp, who develop varying degrees of abdominal distension and whose breathing may be accompanied in expiration by a faintly audible, murmuring whine. The pallor may be so striking that intraperitoneal haemorrhage is suspected. The condition was recognized by Walker and Neligan (1955), who also described it as shock and who recommended the giving of more blood as treatment. In the present investigation the clinical disturbance was unaccompanied by a single biochemical pattern.

Increasing Blood Viscosity. Variation in the viscosity of the blood influences the load carried by the heart (Whitby and Britton, 1953). Any increase in blood viscosity is naturally harmful when it increases the work thrown on a heart with reserves of strength seriously diminished by disease (*Lancet*, 1942). The immediate cause of death from haemolytic disease within 12 to 24 hours of birth is cardiac failure, for which the best immediate treatment is venesection and oxygen administration (Mollison, 1956). The viscosity of blood increases with increase in the haematocrit. For these reasons the wisdom of using packed or sedimented red cells for exchange transfusions may be doubted where the infant's original haematocrit is low and the haematocrit of the donor blood is appreciably higher. The transfusion of anaemic patients was found by Evans (1942) not to increase

whole-blood viscosity, but he transfused with whole blood and the procedure was not comparable in volume or speed with exchange transfusion. No observations on changes in blood viscosity during exchange transfusions with whole blood and with sedimented cells have been found. If the viscosity does in fact rise with a rising haematocrit, then this would provide an objection to the routine exchange of the profoundly anaemic patient's blood with aliquots of sedimented cells. It is acknowledged, however, that if high-output cardiac failure is to be avoided in such infants the haemoglobin value may need to be raised to some extent. This may be done without employing sedimented cells for the whole operation, and it should be done slowly. Any residual anaemia may be corrected later by scalp-vein transfusion when the patient's immediate survival has been assured. At the Simpson Memorial Maternity Pavilion emphasis has always been placed upon leisurely exchange with whole blood and upon the judicious maintenance of a negative balance between withdrawal and replacement in severely affected babies. Rising blood viscosity would be unlikely to bear any relationship to the clinical disturbance of mildly affected infants during exchange transfusion. The blood viscosity of such cases may in fact fall during operation.

In practice, however, there is probably less difference than might be thought between the blood from which the supernatant plasma has been decanted and whole blood which is allowed to stand undisturbed throughout the operation. Recent observations on blood containers in Edinburgh (Cumming, 1957) have shown how very difficult it is to maintain anything like an even suspension of cells in the standard glass transfusion bottles even when these are intermittently inverted.

Cooling

Chilling of the baby during exchange transfusion has been thought to be responsible for some of the abnormalities observed. The rectal temperatures of infants receiving blood at 70°-80° F. have been shown to fall from 97°-99° to 94°-96° in 21 cases studied by Marting *et al.* (1955). Cooling of this degree might occur in newborn infants exposed on a table for two hours unless careful precautions such as those described by Corey *et al.* (1955) are taken to avoid it. Four of the 21 infants, however, showed signs of shock after about 250 ml. had been exchanged. Their blood was noted to be poorly oxygenated, and this was attributed to hypothermia. Two of the four babies died. As a result of their investigation Marting *et al.* produced a glass helix which was immersed in a thermostatically controlled water-bath and through which the donor blood was heated briefly on its way to the baby. The blood reached the infant at a temperature of 96°-100° F. Following this innovation the rectal temperatures of further infants studied were maintained, and their condition was claimed to be better than that of the infants who had received cool blood.

A dramatic description of cardiac arrest during exchange transfusion was given by Pew (1955). An infant with moderately severe haemolytic disease received an umbilical exchange transfusion with very fresh citrated blood. Shortly after 350 ml. had been exchanged the heart stopped suddenly. The infant's chest was opened and the heart massaged. Normal cardiac rhythm was restored after about two minutes. The exchange transfusion was continued and the exposed heart kept under observation. As blood was injected the heart was noted to slow and to be 'definitely cool'; indeed the bradycardia became so profound that further cardiac massage and the intracardiac injection of adrenaline were required. Normal rhythm was again restored; the exchange transfusion was carefully completed and the chest repaired. The total serum calcium concentration shortly after cardiac arrest was only 5·7 mg. per 100 ml. The baby showed some twitching when convalescent. The calcium was not recorded, but the sign disappeared when calcium gluconate was given. No information was provided about the speed of operation or where the tip of the catheter lay. Cooling was considered to be the possible precipitating factor. The first bottle of blood had been adequately warmed, and the crisis developed soon after the second, unwarmed, bottle had been brought into use.

The local application of cold to the front of the chest produces a slow heart rate, diminished systolic output and increased blood pressure (McDowall, 1956). Extracorporeal cooling of dogs down to temperatures of 26° C. will not precipitate cardiac arrest, but the injection of very cold blood close to the heart can provoke auricular fibrillation (Delorme 1957). This would be particularly dangerous if it occurred in an infant with a devitalized myocardium and whose heart was receiving rapidly recurring influxes of 10-20 ml. of blood under pressure.

Autonomic Stress

The catheterization of the umbilical vein and the shunting to and fro of blood in the portal circulation may be more disturbing than has been thought previously. Walker and Neligan (1955) gained the impression that excessive traction on the umbilical cord during manipulation of the catheter produced vomiting. There is no doubt that the prodding of

obstructions within the portal circulation makes the baby retch and he commonly regurgitates. Distension of the portal circulation by rapid transfusion may also precipitate this trouble. Such reflex stimulation was undoubtedly the cause of retching in this small series. Operations in the upper abdomen in relation to diaphragm and peritoneum may provoke hiccup, vomiting and shock. Exchange transfusion evokes dynamic changes in a region richly supplied with both afferent and efferent autonomic nerves and may be expected to give rise to some disturbance.

Inexperience

The experience of those conducting exchange transfusions varies widely. There is more to the procedure than exchanging 10 ml. aliquots of blood. In a surgical team it is unlikely that an operation carrying a comparable mortality would always be left to the house-surgeon or an inexperienced registrar. Yet junior staff may be left unsupervised to carry out an exchange transfusion in the belief sometimes held by senior staff inexperienced in this procedure that normal skill and common sense are all that is required. The apprenticeship to be served by the would-be operator of exchange transfusion is neither short nor easy, and even after many successes the experienced may be humbled by failure. It is interesting to note that Walker and Neligan (1955) had a low mortality, and yet Walker (1955) in a personal communication stated that, taking the country as a whole, the problem of unexpected death was more common than he had previously thought. This suggests that where both skill and experience were available the mortality was lower than in other areas where experience was less. Precisely this view has been expressed by Walker and Mollison (1957). They have shown from national figures that an appreciable number of infants dying of haemolytic disease had received exchange transfusions which were inadequate in volume, and that the actual number of deaths from haemolytic disease in England and Wales was in excess of the estimated annual mortality. Walker and Mollison (1957) calculated that some hospitals might be conducting an exchange transfusion as infrequently as once in four or five months. In such circumstances experience and team-work are hard to obtain. As many as 150 more affected infants might be saved annually if they were to receive exchange transfusion from experienced operators. We also believe that both the morbidity and mortality associated with exchange transfusion may be reduced by experience, and that the latter can be achieved best by centralizing treatment. Smaller obstetric or paediatric units might therefore have to sacrifice their occasional opportunities of carrying out the procedure, but many would be prepared to do so for the sake of the child. In the towns around Edinburgh a number of hospitals make a practice of sending the affected mother to the Simpson Memorial Maternity Pavilion for delivery, and for treatment of the child should that be necessary. By doing so they assure the infants of very early treatment by a team which possesses reasonable experience.

Conclusions

Various clinical disturbances may be observed during exchange transfusion in the infant suffering from haemolytic disease. Exchange transfusion produces considerable change in the patients' plasma electrolytes. The citrate level increases, potassium frequently increases and the calcium-ion level falls irrespective of the total serum calcium. The changes in serum electrolytes were shared by infants who were disturbed and by those who showed no abnormality. The depression of calcium ion can be neither prevented nor corrected by injecting calcium gluconate in the dose employed in this study. Other possible causes of clinical disturbance have been suggested. Evidence for them has not been sought in this study. They include such factors as interference with the circulation during the period of post-natal readjustment, excessive speed of exchange, changing blood viscosity, manipulation of the catheter within the abdomen, the injection of cool blood and, above all, inexperience on the part of the operator.

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TREATMENT OF PERSISTENT ENURESIS WITH THE ELECTRIC BUZZER

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The treatment of enuresis has largely defeated physicians in the past. Some have readily acknowledged this and have pinned their faith on the child growing out of it. Others have used numerous drugs with varying success; since there is a tendency towards spontaneous improvement, and since inert pills are partly effective by suggestion, it has been difficult to assess what specific effect, if any, a particular drug possesses. Psychiatrists have tended to attribute the disorder to infantile regression and have sought, by child guidance techniques, to readjust the child's interpersonal relationships; they have turned a blind eye to the symptom itself, a wise move since it so seldom disappears with such therapy. Nevertheless there is a widespread belief that enuresis is purely psychogenic, a belief which is illustrated by a common mis-spelling 'eneuresis'—as if the condition were a neurosis. Undoubtedly nervous factors influence enuresis (as with epilepsy and asthma) but it is equally true that the cure of bedwetting will often greatly improve the child's emotional state, indicating that the anxiety is secondary, in part at least.

The treatment of enuresis was revolutionized when it was discovered by chance that an apparatus for signalling to the parents that their child had a wet bed and needed changing also had the property of training the child to become dry. Pfaundler (1904) used a quilted pad for the purpose, Mowrer (1938) improved the apparatus by including a relay, and Seiger (1946) first described a metal and rubber pad that could be dried. Subsequently Davidson and Douglass (1950) reported 20 cases in deprived children with 15 cures; Seiger (1952) reported a series of 106 cases, 94 becoming dry for two months or longer, in the majority of cases after less than one month's treatment. Geppert (1953) reported a series of 42 cases with 38 successes using a similar method. Crosby (1950) used the conditioning method but instead of a bell or buzzer he used electrodes attached to the genitalia and loin so that at the start of micturition 'a stimulus, capable of variation to any devised intensity, is applied to the patient'. His results were successful in 52 out of 58 cases.

In view of the intractable nature of enuresis the above results seem almost too good to be true. It is certainly surprising that the medical profession has not adopted the method to any extent in Great Britain, but commercial firms have exploited the treatment on a large scale offering it direct to the public without the supervision of a physician. Only one small series (in deprived children) has been reported and occasional letters (Gillison, 1956) have appeared in the medical press supporting the method. In some quarters there is considerable resistance to it as evidenced by the reply in the *British Medical Journal* (1957) in which the writer, after describing many largely ineffective and blunderbuss remedies, goes on to refer to the conditioning method as 'rather a crude type of therapy'! Since ignorance and prejudice envelop the subject it seemed desirable to collect a series of persistent intractable enuretics to observe how they responded to this form of treatment.

The Apparatus and its Use

One of the reasons why this treatment has not been popular amongst doctors is because of the lack of availability of sets. For some years one firm has been hiring sets for a sum which far exceeds that which the average hospital patient can afford. Recently another manufacturer has begun to produce one which sells at less than half that sum. I have been fortunate in that the father of a former patient has been producing efficient sets which have been sold at less than one-fifth the cost of hiring. Furthermore, through the generosity of the Chamberlain Foundation, I have been able to lend a similar set free of charge to those parents who were unable to buy one.

The apparatus consists of an alarm unit containing a buzzer, light, relay and 6-volt battery together with two flexible leads that can be clipped on to two fine metallic rectangular gauze mats about 16 × 20 in. The mats are best secured on the bed by slipping each into a pocket obtained by sewing a pillowcase to a drawsheet along

its three closed sides to make a double open-ended pocket. The child, preferably devoid of pyjama trousers, lies above the linen sandwich containing the mats. The alarm unit stands on a table or chair close to the bed and is switched on at bed time. The alarm is actuated when the circuit is completed by urine that has soaked through the layers to reach the lower of the two mats. Occasionally a 'dry ring' is obtained if the mats inadvertently touch (frayed ends of wire may traverse the intervening material) or if the patient sweats profusely. Conversely, the alarm may fail to sound if a clip becomes dislodged by a restless sleeper. Normally, however, a teaspoonful of urine will suffice to start the buzzer and this, by awakening the child, will bring an end to micturition and will eventually, in favourable cases, prevent the act starting at all. The size of the wet patch indicates how quickly the child has awakened. In a typical response the size of the patches diminishes as the training takes effect but sometimes the child is such a heavy sleeper that all the patches remain large because he is not awakened by the buzzer (another member of the family may have to switch it off). In such cases a louder bell can be plugged into the set or dexamphetamine can be prescribed as well but these additional measures are seldom required. When the alarm sounds and the child awakens he is instructed to switch it off, get up and finish passing urine. In very bad cases it is desirable to re-set the apparatus using a dry drawsheet ensemble but in the majority one alarm per night is sufficient.

The Series

In the past five years over 500 enuretic children have been referred to my out-patient clinics. Many of them have responded to simple forms of therapy and many others have recovered spontaneously but gradually a hard core of resistant cases accumulated. They were treated with the electric buzzer, the only criteria for selection being that they were old enough, sufficiently severe, and resistant to other forms of therapy. There were only nine omissions from a consecutive series of 109 cases selected for treatment and provided with an apparatus: in four the parents refused to report progress, in two the children (aged 10 and 12) refused to use the apparatus, in two the parents were too stupid to be able to work it and in one the boy stopped wetting before the set was put into use.

The series therefore consists of 100 persistently enuretic children consecutively supplied and treated with a conditioning apparatus. It is important to emphasize that inclusion was by enrolment rather than by completion of treatment. Since the successes are usually rapid, a better rate of cure could have been obtained by discarding those in whom the treatment is incomplete.

Age. There has been a tendency to provide older children with this treatment partly because they have usually resisted many others and partly because they are more likely to cooperate. A few young ones have been included, usually because they had inherited a set after an older sibling had completed treatment. In general, however, the use of an apparatus under the age of 7 has not been recommended and it will be seen from Table 1 that 74 fall within the 7-13 bracket, 14 being younger and 12 older than this group.

Sex. There is general agreement that males predominate in any series of enuretic children and this has been the case here. Only 19% were girls.

TABLE 1

AGE AT START OF TREATMENT AND SEX

Age in Years	Total	5–7	–9	–11	–13	–15	–17	17+
Male ..	81	12	18	19	22	7	2	1
Female ..	19	2	4	8	3	2	—	—
Total ..	100	14	22	27	25	9	2	1

Onset. In the vast majority enuresis had been present since birth and the longest dry spells (if any) before treatment had seldom exceeded one week. In five cases enuresis had begun, after a long period of dryness, at the age of 4 years or older; in two others it had been very infrequent until the age of 5. Four mothers stated that there had been a dry spell at least six months long between the ages of 1 and 3 years—a difficult fact to explain. Two boys had been dry for four and five months respectively after treatment with a conditioning apparatus obtained elsewhere; they were therefore relapses but entered this series as new cases because their parents could not afford to hire a second apparatus.

Family History. For the purpose of this enquiry, enuresis was regarded as having been present if bedwetting had occurred above the age of 5 years. A positive history in a close relative (parent or sibling) was obtained in 47 cases (one or both parents in 30, one or more siblings in 17, parent and sibling in ten). The history relating to enuresis in the patients' parents was not complete in 18 cases but in six a more distant blood relative had been affected. A negative history in near relatives was obtained in 35 cases with complete records but in 22 of these it was positive in more distant relatives (aunts, uncles and first cousins). These findings indicate that about 50% of cases have a positive family history and a further 30% have blood relatives affected by the disorder.

Intelligence. In this series the great majority were of average intelligence. Eight were above, nine were below and one was educationally subnormal.

Nervous State. Parents were asked if the child had any other nervous troubles. In 30 they were absent and in 70 they were present, being very severe in five. (In an unselected series of children starting school 50% were stated to be nervous, but this is a younger age group.)

Investigations. All the children were medically examined and their urine tested. Twenty-eight of the first 50 cases in the series and 17 of the second 50 had been fully investigated by means of micturating cysto-urethrograms, cysto-urethroscopy, pyelography, etc. This falling off in zeal for investigation was due to a change of policy whereby latterly only failures were investigated. In two cases this was refused.

Previous Treatment. Almost every patient had failed to respond to weeks or months of drug therapy which had extended for over one year in 29 and was continuous for five years in one. Three were referred from child guidance clinics and one other had failed to respond to that kind of treatment. One successful case had previously attended a faith healer for many months. As already stated, two had relapsed following this form of therapy.

Results

It soon became apparent that successful cases usually responded rapidly. This led us to use the total number of wet nights during the third month as a criterion of early response which subsequently proved to be a reliable index of the final outcome.

TABLE 2
EARLY RESPONSE CORRELATED WITH SEVERITY OF ENURESIS

Total No. Wet Nights During 3rd Month	Total	Severity of Enuresis Before Treatment (Approximate Proportion of Wet Nights)			Group	
		<50%	50%–75%	75%–100%	Charity	Private
Nil ..	44	5	15	24	25	19
1–3 ..	10	2	1	7	6	4
4–6 ..	14	2	3	9	10	4
7+ .	17	1	3	13	12	5
Abandoned	7	1	3	3	5	2
Not known	8	2	2	4	4	4
Total ..	100	13	27	60	62	38

In Table 2 the early response is correlated with the frequency of wetting when treatment was first started. Infrequent wetting means that the training effect is seldom applied. Hence children who were wet appreciably less than 50% were not treated in this way and those in this group did rather less well than the average. In the worst group the results are also suboptimal because concealed within it were several children who were wet more than once each night and hence had further to go to become dry. The best results were therefore obtained in the group with 50 to 75% wet nights at the outset, for 59% had fewer than four wet nights in the third month compared with 54% and 50% in the other two groups.

Also in Table 2 a distinction is made between those who bought an apparatus and those who borrowed one free of charge. The latter group included many with very low social standards which perhaps explains why they achieved less good results. Taking all the cases which were wet fewer than four times during the third month, there were 23 out of 38 (60%) who bought their own sets compared with 31 out of 62 (50%) who borrowed one.

TABLE 3
LATE RESULTS CORRELATED WITH EARLY RESPONSE

Total No. Wet Nights During 3rd Month After Starting Treatment	Total	Final Assessment (4 mth.–2 yr.)			
		Dry	Occasionally Wet	Improved	Failed
Nil	44	38	5	—	1
1–3	10	7	3	—	—
4–6	14	3	5	4	2
7+	17	1	1	3	12
Abandoned	7	—	—	—	7
Not known	8	1	1	2	4
Total	100	50	15	9	26

In Table 3 the late results are correlated with early response. The successful 65 cases have been followed up for a period ranging from four months to well over one year; it exceeded six months in 43 cases of which 15 were followed up for more than one year.

Of the 50 cases finally classified as 'dry', 38 became completely dry before the third month of treatment began, whereas only one was ultimately cured when the number of wet nights in the third month exceeded seven.

In addition to the 50 dry cases, 15 children have been classed as 'occasionally wet'. They had on an average one or two wet nights per month after treatment was completed. As might be expected, the early response tended to be less rapid in this group.

The nine classified as 'improved' each showed a marked reduction in the amount of wetting but at the final assessment there was still appreciable

wetting. Thus one child was wet 19 times during the first week of treatment but steadily improved so that in the 32nd week he was only wet twice.

Eighteen of the failures failed to respond appreciably. One responded at first but then relapsed and continued to wet frequently; he lived in a very poor home and had no bed of his own. To these failures must be added seven in whom the treatment was abandoned before the end of the third month, making a total of 26 failures.

Younger children did slightly better than older ones, the average age of the successful cases being 9 years compared with 11 years for the 26 failures.

There were too few children of below average intelligence from whom to draw definite conclusions but the impression has been gained that those with lower intelligence respond less rapidly.

Relapses. There were nine cases in which relapses requiring a refresher course occurred and eight responded rapidly and completely. One had been completely dry for nine months before relapsing. No doubt as further time passes other relapses will require treatment. In most cases the relapse was clearly related to an infection, fatigue or anxiety over examinations at school. Even some of the children classified as 'dry' experienced an isolated wet night in such circumstances but they were very rare.

Pattern of Response

The mechanism of the treatment is clearly one of training; in a favourable case the number of wet nights steadily diminishes and at the same time the size of the wet patch gets smaller indicating that the child is waking up more quickly. This is well illustrated by the following typical case history:

L.C., a boy aged 11 years, had never had a dry night all his life. He was of average intelligence, not nervous, a restless sleeper; his maternal grandmother, mother and brother had all been bedwetters. Drug therapy had not helped him. His response was as follows:

Weeks	Wet Nights	Size of Patch
1st	7 (twice one night)	3 large
2nd	4	All small
3rd	2	Both small
4th	1	Small

The set was then removed from his bed and he has been followed up for eight months but has never since been wet. Occasionally he has to get up in the night to pass urine.

Some children find that they have to get up at night in order to keep dry but as their confidence increases the necessity diminishes. If, however, they are ill or tired they may fail to do so and wet the bed. Forty-one successful cases replied to a questionnaire which revealed that 27 never got up in the night, eight occasionally did and six usually or always did. Some parents who were enuretic in childhood still had to get up to micturate each night indicating that nocturnal frequency persisted.

Failures

It would be tedious to give details of all the failures. Probably lack of cooperation is the commonest cause; thus of the eight in whom no detailed reports for the first three months were available, four were failures. Parents were usually to blame and in a few cases treatment was started in hospital in an effort to avoid this. In one case treatment had to be abandoned because the county M.O.H. forbade us to treat him in the residential home where he lived because a psychiatrist advised against this form of therapy and recommended an alarm clock instead! One juvenile delinquent was responding well in hospital but absconded before treatment was completed because he learned that he was wanted by the police. Two mothers were definitely psychotic. Very heavy sleepers were not awakened but this was sometimes overcome by administering dexamphetamine for a time as well. In one case this failed and so did vibrators attached to his forehead; perhaps an electric shock would have roused him but it was not considered justifiable. Some were awakened but failed to be trained so that the number of wet nights did not diminish though the bed was less soaking. In three cases an initial response was followed by a return to the original frequency suggesting an active resistance to the treatment, probably emotionally determined. We aimed at keeping the child on the set until four consecutive dry weeks had been achieved but one educationally subnormal girl aged 13 refused to use it for more than one week and a boy complained that the neighbours heard the buzzer and he resented the publicity that this entailed.

Conclusion

The fact that a favourable response was rapidly obtained in 65 out of 100 severe enuretics speaks for itself. The marked improvement in the mental outlook of these cases was most gratifying. Several parents reported that their children were happier and more confident now that their enuresis had been eliminated. It is clear that a great deal of the associated anxiety was secondary to the enuresis and disappeared with it. There can be no doubt

that psychological aetiological factors have been greatly exaggerated in this disorder, though they certainly play a part in aggravating it. Probably they are of the same degree of importance in enuresis as in asthma, migraine and epilepsy, disorders, incidentally, with which it is frequently associated. In my opinion it is fully justifiable and very rewarding to tackle the symptom directly by the conditioning method, a triumph for therapeutic behaviourism.

Summary

One hundred intractable severe persistent enuretics have been treated by the conditioning method.

There were 81 boys and 19 girls aged 5-17 years.

Fifty responded rapidly and completely, 15 dried up almost completely, nine improved markedly but slowly and 26 were failures.

The pattern of response and the reasons for failure are described.

A positive family history was obtained in 47 and more distant relatives were enuretic in a further 28 cases but the records were not all complete.

Successful cases frequently showed definite improvement emotionally. The importance of psychological factors in causing enuresis of this type has been greatly exaggerated.

Relapses were mainly provoked by infections, sometimes by fatigue and anxiety.

I am most grateful to the Chamberlain Foundation for so generously providing me with sets to lend to patients unable to afford to buy one. The Foundation distributed them through the International Office Service, Ltd., 30 City Road, London, E.C.1.

I am also indebted to Mr. M. P. Curwen, statistician, St. Bartholomew's Hospital, for his help with the presentation of the results.

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RECURRENT ABDOMINAL PAINS: A FIELD SURVEY OF 1,000 SCHOOL CHILDREN

BY

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What sort of children are they who complain of recurrent abdominal pains, and how do they compare with children who do not suffer from such pains? Because patients referred to hospital are inevitably pre-selected, we have tried to answer these questions by a survey of 1,000 unselected children at primary and secondary modern schools.

One of us throughout the survey, and sometimes both, attended routine school medical examinations at Bristol from January, 1955, to June, 1956. A few children not accompanied by a parent were excluded; the remainder were asked if they suffered from bouts of abdominal pain.

Nature of Investigation

Children with Pains. In our series we included every child who had had at least three bouts of pain, severe enough to affect his activities, over a period of not less than three months, with attacks continuing in the year preceding the examination. In taking the history, which was obtained from the mother as well as the child, we went into considerable detail regarding home life and the family as well as the child's personal history. The school headmasters and headmistresses helped greatly by providing reports on behaviour, intelligence and attainments.

Children with pains were examined clinically, but ancillary investigations were not undertaken (it is intended to publish separately a complementary investigation of hospital cases). The single exception was electro-encephalography (E.E.G.), for which facilities were made available at a convenient centre.

Control Series. Detailed information on the same lines, *i.e.*, personal and family history, as well as clinical examination and E.E.G., was obtained from a proportion of the children living in the same districts and attending the same school medical examinations, but not found to be complaining of abdominal pains. As a rule the child who happened to be next on the list after one with pains was chosen for the control series. The numbers were, however, considerably increased by adding further children as often as time permitted, and by including a small number of those below school age who by chance had come with their mothers.

Incidence

When 1,000 children with their mothers had been questioned the investigation was stopped. The numbers obtained are summarized in Table 1.

TABLE 1
CASE MATERIAL

	Total	Boys	Girls
Preliminary Questioning	1,000	528	472
Detailed Questioning and Examination:			
Recurrent abdominal pains*	108	50	58
Controls	312	155	157

* Thirteen children whose pains had ceased more than a year previously have been excluded here and from the calculations of incidence.

Of the total, 10·8% had recurrent abdominal pains fulfilling our criteria. Girls were affected more often than boys (12·3% to 9·5%).

Age Distribution. There was considerable variation in the incidence of pains at different ages (Fig. 1). There were no complaints of pains in the small number of children below 5 years of age. In boys from 5 to 10 years of age there was a steady incidence of between 10% and 12%, followed after a fall by a late peak at 14 years. In girls the incidence was similar up to the age of 8 years. This was, however, followed by a marked rise, with more than a quarter of all girls of 9 years affected, and subsequently a steady decrease.

Age of Onset. The age of onset of the pains in 118 children is illustrated in Fig. 2. (The total of

118 is made up of 108 children with continuing pains and 13 in whom pains had ceased more than a year previously, less three in whom the age of onset was not known.)

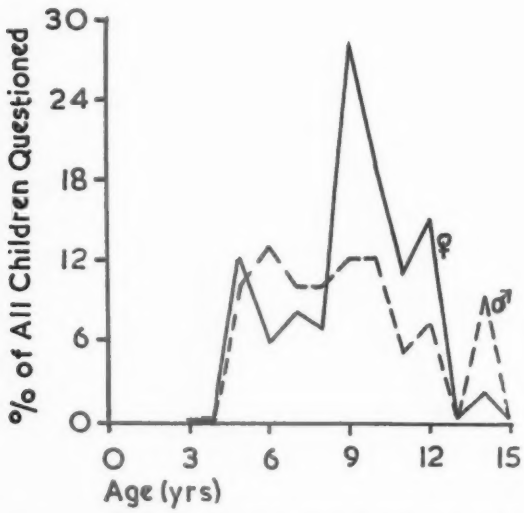

FIG. 1.—Proportion of children affected at each year of age.

In both boys and girls there was a steady rise up to the age of 5 years. In the boys the numbers then fell; but in the girls there was a further striking rise, with pains commencing in a large proportion between 8 and 10 years of age, and none subsequently.

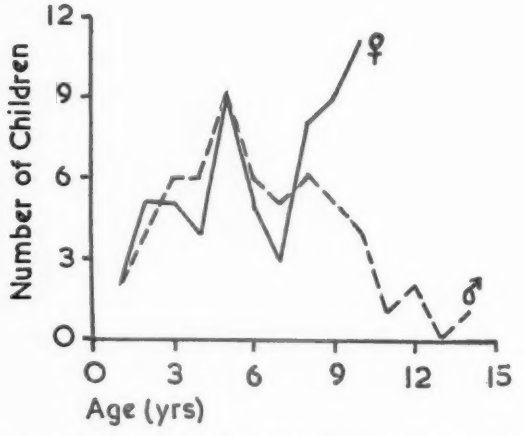

FIG. 2.—Age of onset of pains. (118 children: 57 boys, 61 girls.)

The Pains

A full description of variations in the characteristics of the pains will not be given here. We have found elsewhere (unpublished hospital data) that an accurate description of pain in children is more likely to be obtained during attacks than in the intervals.

In brief, it seemed that in some two-thirds of the children the pain was felt at or round the umbilicus. With only a few exceptions, it occurred in the mid-epigastrium among the remainder. In about a quarter it was severe. The time of occurrence varied greatly. The duration of the pain showed great variability from case to case, and from one bout to another in most children. The frequency of occurrence also varied considerably, from those with a rare (often severe) episode to those who said they nearly always had some (usually mild) pain. About one-fifth showed a tendency to periodicity.

The pains were attributed to many factors. The most common were excitement, worry or 'being worked up', feelings often associated with schooling. One girl had a severe attack on the day after she lost a pound note which a neighbour gave her to buy cigarettes. As 'cures', soda-water, defaecation and the doctor's medicine came low in the list. Rest was often thought helpful, but in most cases the pains just got better.

Table 2 summarizes the disturbances associated with attacks of pain.

TABLE 2
DISTURBANCES ASSOCIATED WITH ATTACKS OF PAIN

	%
Pallor	38
Vomiting	22
Fever	11
Headache	23
Subsequent sleepiness or lethargy	26

The association was scored only if it occurred commonly or invariably. Several might occur together, and in a fifth of the cases (often those with severer pains) the combination of abdominal pain, vomiting and headache, and sometimes fever, was recorded. There were in addition 13 children who had bouts of headache and vomiting without abdominal pains.

As between the isolated abdominal pain and the combination of many disturbances, there seemed to be a gradation from case to case, which made any clear-cut grouping unprofitable. In any individual child the pattern tended, however, to be more or less constant, though with occasional variations in severity.

Family History

The child is an inseparable part of his family, and we were particularly interested in comparing the families of children with pains against those without pains. Table 3 summarizes some relevant data from the family histories.

TABLE 3
DATA FROM FAMILY HISTORIES

Complaints of other Members of Family	Percentage in Children With Pains	Percentage in Children Without Pains
Recurrent abdominal pains ..	46	8
Peptic ulcer	10	3
Appendicectomy	8	3
Migraine	14	3
Nervous breakdown	10	2
Fits	6	3

We have included only the immediate family, *i.e.*, parents and siblings, though the data of more distant relations showed similar trends. In the diagnoses listed we have not attempted to be precise, since the sources of our information were non-medical. Thus, under 'peptic ulcer' we included only those in whom there was said to have been a haematemesis or operation, or radiographic confirmation; under 'migraine' we included all severe headaches; and under 'nervous breakdown' disorders severe enough to have caused a serious disruption of normal life. Mothers accounted for two-fifths of those members of the family affected by recurrent abdominal pains, fathers a slightly smaller proportion, and brothers and sisters the remainder.

A marked preponderance of the disorders listed was found in the families of children with abdominal pains, though the figures for 'fits' are too small to be statistically significant. It is clear that the families of these children have an enhanced tendency to abdominal and 'nervous' disorders. In other respects, including psychosis and serious behaviour disorders, the numbers were very small and we found no obvious differences from the controls.

An additional item was the proportion of 'broken homes', *i.e.*, where one or other parent was dead, or had left home, or there had been a divorce or legal separation. We recorded a 'broken home' in 4% of the children with pains, as, rather unexpectedly, against 7% of the controls.

Child's History

Some noteworthy differences also emerged when we compared the histories of children with and without abdominal pains (Table 4).

TABLE 4
DATA FROM PERSONAL HISTORIES

	Percentage in Children With Pains	Percentage in Children Without Pains
Appendicectomy	5	0·3
Tonsillectomy	24	26
Frequent headaches	14	5
Bilious attacks	12	5
Habitual constipation	5	3
Fits	2	6
Asthma	6	2

Appendicectomy in the control series was rare (1 in 312). The histories of five children with recurrent abdominal pains in whom appendicectomy was performed were obtained and are summarized herewith.

Case 1. Colicky pains for nine months. 'Normal looking appendix' removed. Pains recurred.

Case 2. Pains for several months. Operation because of tenderness in R. iliac fossa. Normal appendix removed. Pains recurred.

Case 3. Pains for several years. 'Mildly infected appendix' removed. No further pains when seen two years later.

Case 4. No previous pains. Operation at 2 years of age. Acutely inflamed appendix (and pelvic abscess) removed. Recurrent abdominal pains during the ensuing seven years.

Case 5. Four attacks of abdominal pain in two years. In the fifth attack pain became localized for the first time to the R. iliac fossa, with overlying rigidity. Acutely inflamed retro-caecal appendix removed. No further information available.

Tonsillectomy was the only other operation done with any frequency; the incidence was almost identical in the two groups.

The children with abdominal pains suffered more than the controls from headaches and from so-called bilious attacks. The comparative figures for constipation, fits, asthma and allergic conditions in general were too small to warrant conclusions. The history of other physical disorders showed no significant differences between the two groups.

Physical Assessment

We assessed the children of both groups by recording items like physique, posture, height, weight, colouring, palpable lymph nodes, condition of the teeth and tongue, and all abnormalities found on routine clinical examination. The average weights of the younger children with pains were less by 1 to 2 lb. than those of the controls; the numbers of older children were too small for definite conclusions. In other respects, including height, there were no apparent differences.

Intelligence

For the assessment of intelligence we relied on school reports, based on the child's ability, progress and attainments. On this basis children are allocated to one of the school educational 'streams'. We have presumed that errors inherent in such a method are equally applicable to both groups of children and do not affect the validity of a comparison between

them. Table 5 shows that the two groups are almost identical.

TABLE 5
INTELLIGENCE ASSESSMENT

Educational Stream	Percentage in Children With Pains (No: 120)	Without Pains (No: 221)
A	20·8	21·2
B	28·3	28·0
C	32·5	32·1
D	16·6	16·3
E	1·6	2·2

Emotional Disturbances

From information given by the parent, schoolmaster and child, we compared the frequency with which some common complaints which might reasonably be attributed to emotional disturbances occurred in the two groups of children. Table 6 shows those groups in which there was a significant difference.

TABLE 6
SOME EXPRESSIONS OF EMOTIONAL DISTURBANCE

Disturbance	Percentage in Children With Pains	Without Pains
Undue fears	27	10
Nocturnal enuresis	20	8
Sleep disorders (including nightmares)	39	18
Appetite difficulties	37	21

Among appetite disorders we inquired particularly about milk-drinking habits, because of the suggestion that excessive milk drinking may be associated with abdominal pains. We found that children with pains tended to drink not more, but rather less than the controls. In other respects, like nail-biting and tics, there were no apparent differences.

Personality

From the information available we tried to group the children with or without pains according to their personality traits. The findings are summarized in Table 7.

TABLE 7
PERSONALITY TRAITS

Trait	Percentage in Children With Pains	Without Pains
Normal, average, good ..	51	80
Hostile, anti-social, unreliable	5	5
Aggressive, quarrelsome, jealous	6	2
Passive, negative	4	5
Highly-strung, fussy, excitable	21	4
Anxious, timid, apprehensive	13	4

As compared with the controls, many more of the children with pains tended to be highly-strung, fussy, excitable, anxious, timid and apprehensive. We formed an impression of over-conscientiousness in many children with pains, and also in their parents. More of these children, too, were said to be 'bad mixers' (23% as compared with 15% of the controls).

Electro-Encephalography

With the cooperation of the parents we took this opportunity of obtaining E.E.G.s from many children without pains and comparing the findings with those of children in the same range of ages but with recurrent abdominal pains. E.E.G.s were obtained from 202 school children without pains and 97 with pains (Table 8). The reports, both on children with abdominal pains and on the controls, were made by Dr. E. C. Turton without knowing into which group they fell.

TABLE 8
REPORTS ON ELECTRO-ENCEPHALOGRAMS

E.E.G. Record	Percentage in Children With Pains (No: 97)	Without Pains (No: 202)
Normal	74	74
Normal but immature for age	12	9
Organic abnormality	0	0·5
Localized slow activity ..	0	0·5
Focal spikes	4	1·5
Epileptiform	10	14·5

In the epileptiform group were included all definite and borderline cases, whether in resting or evoked (photic stimulation and hyperpnoea) records. The classification of normal records was based on accepted descriptions for children (*e.g.*, Henry, 1944). Children with a history of fits were included: there were two with abdominal pains (neither had had fits for several years) and 12 without pains (including three continuing under treatment for fits).

Discussion

Incidence. The high incidence of recurrent abdominal pains in our unselected school population confirms the impression that this is one of the commonest of childhood complaints. Our material was drawn from working and lower middle class families, in a thriving town with a population approaching half a million and negligible unemployment. We have no means of comparing the incidence with that in either agricultural communities or in the higher social and financial scales.

Naturally, the incidence must vary according to the criteria used in the selection of cases. Ours

were chosen with the object of ruling out trivial and transient disturbances, on the one hand, and, on the other, serious organic disorders which would be expected to have become manifest in the time limit we set. The series of children with pains proved similar to another series of children referred to hospital with the same complaint (unpublished data). The significant differences found were that in children attending hospital because of abdominal pains the proportion with severe pains is slightly higher, there are more 'only children', and there are proportionately fewer girls in the pre-pubertal age-group.

On these grounds we consider that our conclusions are, in the main, applicable to the vast numbers of children with this common complaint.

Age Incidence. The age incidence and the age of onset of pains in our series set some interesting problems which remain to be solved. In the early years the curves for both sexes are similar, suggesting that the underlying factors are the same for both. It is of interest that the peak occurs at the age when schooling commences. From the age of 8 years the pattern diverges markedly in the two sexes, and the onset of puberty in girls might be postulated as an additional factor. From our data we cannot confirm or refute this possibility. As between girls with or without pains, there was no disparity in the time of development of secondary sex characters; and the number in whom the menarche had occurred was so small as to be non-contributory.

Organic Disorders. It is obviously important to determine or eliminate organic disease as a cause, though in many large published series the proportion of children with a demonstrative causative organic disorder has been shown to be small. In the present study, on clinical examination we found no appreciable physical differences between children with or without pains, other than a slight disparity in average weight. Even this may reasonably be related to the appetite disturbances which are commoner in children with abdominal pains.

The figures for epileptiform abnormalities in the E.E.G.s of our two groups lend no support to the notion that the recurrent abdominal pains which are so common in childhood are an expression of epilepsy without fits.

Emotional Disorders. Under this heading fall the significant differences between our groups of children with or without pains. Children with certain types of personality seemed commonly affected. They were timid, nervous, anxious or over-conscientious—just the types of children in whom emotional disturbances would be expected to develop. In children with an underlying predisposition school or other difficulties often seemed to have a 'trigger effect' in evoking pains.

Family History. High though they are, our figures for the incidence of abdominal pains in the families are almost certainly an underestimate. We have found elsewhere that the proportion of positive replies increases if the number of interviews is increased and the parents are given better opportunities to remember. But even as they stand the figures illustrate the continuing thread of disorder in successive generations. Our data contribute nothing to the fascinating problem of why perhaps only one among several children, with a common family background, should develop abdominal pains.

The relatively high incidence not only of functional but also of organic abdominal disorders in the families of children with pains is of great interest. Is it that these 'abdominally minded' families are more thoroughly investigated? Have these families a predisposition to abdominal disorders of different sorts? Does functional disorder develop into organic disease? In this connexion we mention two parents who, like their children who were in our series, had complained of abdominal pains in childhood, and who now suffer from peptic ulcer in adult life. Similar examples will probably occur to most doctors, but they must be considered and weighed against the high frequency both of abdominal pains in childhood and of peptic ulcers in adult life.

Conclusions

We set out to compare children complaining of recurrent abdominal pains against children without them, in a large, unselected group of school children. In our survey three subsidiary points were established: *First*, the high incidence of recurrent abdominal pains, especially at certain ages and particularly in girls. *Second*, the high incidence of abdominal and certain other complaints in the families of affected children. *Third*, the negative evidence of any physical association with the pains, and the positive evidence of frequent emotional disturbances.

Children with abdominal pains tend to fall into certain categories as regards personality and emotional patterns, so much so that often one can forecast which children are likely to develop the symptoms. Often when difficult situations are imminent, as at the beginning of school terms or examinations, the occurrence of pains can be correctly predicted. As compared with other

children, those with pains tend to be anxious, timid, fussy and over-conscientious, taking the ordinary difficulties of life (especially of school life) too much to heart.

We gratefully acknowledge our indebtedness to Dr. A. L. Smallwood, Senior School Medical Officer, and other School Medical Officers in the Bristol area, and to the Chief Education Officer and his staff, including the headmasters and headmistresses who cooperated so generously and made our survey possible, and to Dr. E. C. Turton for the E.E.G. reports.

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SALMONELLA MENINGITIS

BY

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Meningitis due to organisms of the salmonella group is a relatively uncommon condition but is of importance because of the very high mortality rate which has been recorded. The first case of meningitis due to this cause was reported by Ghon (1908) and was due to *Salmonella paratyphi B*. The literature since that time has been reviewed by several authors including Bahrenburg and Ecker (1937) who reported 34 cases, Ramón Guerra, Peluffo, Laguarda and Aleppo (1939), Henderson (1948) and Beene, Hansen and Fulton (1951). Henderson (1948) has produced the most comprehensive review of the subject and quotes 144 cases, including three of his own, due to *S. panama*, *S. newport*, and *S. typhi-murium* respectively. The report by Beene *et al.* (1951) includes a further 87 cases not referred to by Henderson. These include 17 cases due to *S. typhi* which Henderson specifically excluded from his review. These authors also include a case of their own due to *S. montevideo*, the first recorded case due to this organism.

Three epidemic outbreaks in newborn infants have been reported. Guthrie and Montgomery (1939) discuss 12 cases due to *S. enteritidis*. In each one there was diarrhoea with vomiting, convulsions, coma, and a fatal termination. Post-mortem examination showed a purulent meningitis associated with catarrhal enteritis. Curbelo and Martinez Cruz (1941) reported 21 cases in newborn infants in an explosive-type outbreak in Cuba. Here the causative organism was *S. havana* and again there was a fatal outcome in each patient. High and Spaulding (1946) recorded a further outbreak involving ten infants, due to *S. panama*, again with a 100% fatality rate.

During the past 18 months four cases of salmonella meningitis have been encountered in this hospital. Two of these have been due to species of salmonella not previously reported as having been found in the cerebrospinal fluid, namely, *S. johannesburg* and *S. heidelberg*.

Reports of Cases

Case 1. M.P., a female Bantu infant aged 11 months, was admitted to hospital with a history of loss of appetite and general malaise. The child had recently had an attack of whooping cough complicated by bronchopneumonia and had apparently not fully recovered. No further details were obtainable from the relatives.

On examination, the child appeared listless and apathetic. The temperature was 103·0° F. and the pulse rate 130 per minute. The skin showed some signs of dehydration but the anterior fontanelle was tense and bulging. There was marked neck stiffness and Kernig's sign was positive. The deep reflexes were equal and brisk. The ocular fundi appeared normal. Examination of other systems was essentially negative. Shortly after admission the child had a number of generalized convulsions.

Lumbar puncture showed a turbid fluid under greatly increased pressure. Queckenstedt's test gave a normal response. The fluid had the following composition: protein, 200 mg. %; sugar, 10 mg. %; globulin (Pandy's test), greatly increased; chlorides, 670 mg. %; lymphocytes, 120 per c.mm.; polymorphonuclear leucocytes, 620 per c.mm. A Gram stained film of the fluid showed the presence of many Gram negative bacilli. Culture of the fluid resulted in the isolation of an organism of the salmonella group. Further examination of it showed its antigenic structure to be IV, V, XII : r—1, 2, 3, which is that of *S. heidelberg*. Sensitivity testing *in vitro* by the dried disc method showed the organism to be sensitive to chloramphenicol, streptomycin and the tetracycline group of antibiotics.

Treatment was begun on the day of admission with 0·25 g. of streptomycin intramuscularly followed by 0·25 g. twice daily. Chloramphenicol, 125 mg., was also given intramuscularly followed by 125 mg. every six hours. During the subsequent ten days there was little change in the clinical state. The cerebrospinal fluid four days after admission was sterile. In view of the poor response, chloramphenicol was discontinued after ten days and tetracycline, 125 mg. intramuscularly every six hours, was given instead. Again there was no improvement under this regime and culture of the cerebrospinal fluid in the third week of illness gave rise to a heavy growth of *S. heidelberg*. There was a gradual deteriora-

tion in the infant's condition and death took place one month after admission. Permission for necropsy was refused.

Case 2. M.D., a male Bantu infant aged 5 months, was admitted with a history of diarrhoea of one month's duration. No further clinical history was obtained. The child was in a state of coma with a temperature of 102·6° F. and a pulse rate of 126 per minute. There was a pronounced squint and marked neck stiffness with a positive Kernig's sign. Examination of the lungs showed signs suggestive of bronchopneumonia. Examination of other systems was negative.

Lumbar puncture on admission showed a turbid fluid under increased pressure. The fluid had the following composition: protein, 500 mg. %; chlorides, 670 mg. %; sugar, 47 mg. %; globulin, marked excess; polymorphonuclear leucocytes, 800 per c.mm. and lymphocytes, 120 per c.mm. Gram stained films showed large numbers of Gram negative bacilli. Culture of the fluid resulted in the isolation of an organism of the salmonella group. Subsequent antigenic analysis showed its structure to be as follows: I, IX, XII : g, p-, which is that of *S. dublin*.

The child died some 20 minutes after admission. Necropsy examination showed an extensive purulent meningitis. There was a moderate degree of fatty change in the liver and areas of bronchopneumonic consolidation were present in both lungs.

Case 3. S.J., a 4-month-old female Bantu infant, was admitted to hospital with a two weeks' history of diarrhoea accompanied by vomiting. No further details were available from the relatives apart from the fact that she had been in hospital one month previously with a similar complaint.

The child was in a moribund state. The temperature was 103·2° F. and pulse rate 126 per minute. The respirations were rapid and coarse crepitations were present in the right mid-zone. The anterior fontanelle was tense and bulging. The eyes were deviated to the right side and there was a marked degree of neck retraction and some degree of opisthotonos. Kernig's sign was positive. Both upper and lower limbs were very rigid. The deep reflexes were brisk. The pupils were equal, central and reacted to light. The spleen was palpable one finger breadth below the costal margin. Examination of other systems was negative.

Lumbar puncture was performed but only a small quantity of fluid was obtained by aspiration. Queckenstedt's test indicated the presence of a block. Examination of the fluid revealed a large number of polymorphonuclear leucocytes and numerous Gram negative bacilli. There was a marked excess of globulin but insufficient fluid was available for further biochemical investigation. Culture of the fluid resulted in the growth of an organism which on further investigation was found to be a salmonella with the following antigenic structure : I, XL : b—e, n, x. This is the antigenic formula of *S. johannesburg*. The organism was sensitive *in vitro* to chloramphenicol, streptomycin and the tetracycline group of antibiotics.

On admission the child was given 500,000 units of penicillin intramuscularly. Following the report of a probable salmonella infection chloramphenicol therapy was begun the next day with 250 mg. intramuscularly and then 250 mg. every six hours. Streptomycin, 0·5 g., was also given intramuscularly. The child's condition was critical, however, and death occurred the following day. Permission for necropsy was refused.

Case 4. T.X., a 3-year-old female Bantu child, was admitted to hospital with a history of having had a convulsion during sleep a few hours earlier. The convulsion had involved all limbs equally and since then the child had been in a state of coma. Before the onset of the convulsion the child had apparently been quite well. No previous history of convulsions was admitted and the past medical history was negative.

The child was in coma with a temperature of 105·0° F. and pulse rate of 118 per minute. She was having almost continuous convulsive movements involving all four limbs but especially marked on the left side. The head was rotated to the left. The pupils were dilated and did not react to light. There was no evidence of neck retraction and Kernig's sign was negative. The deep reflexes on both sides were brisk and the plantar responses were flexor in type. There was bilateral purulent conjunctivitis. Examination of other systems was negative.

Lumbar puncture revealed a purulent fluid under increased pressure containing: protein, 500 mg. %; chloride, 700 mg. %; sugar, 70 mg. %; globulin, marked excess; polymorphonuclear leucocytes, large numbers. Gram stained films showed many Gram negative bacilli. Culture of the fluid resulted in the isolation of an organism giving the biochemical reactions of a salmonella. This organism, however, was in a rough phase and all attempts to obtain the smooth state were unsuccessful. Consequently the antigenic formula is in doubt. The organism was sensitive *in vitro* to chloramphenicol, streptomycin, and the tetracycline group of antibiotics.

Chloramphenicol, 250 mg., was given intramuscularly followed by a similar dose every six hours. During the following few days the child developed marked signs of meningeal irritation with neck retraction and a positive Kernig's sign. There was little improvement in the clinical state for a period of some three weeks during which time she remained pyrexial. The causative organism was still present in the cerebrospinal fluid one week after admission but the fluid became sterile on the tenth day. After three weeks there was a gradual slow recovery complicated at one stage by the development of measles. The child was discharged three months after admission apparently cured.

Discussion

Salmonella organisms infecting the leptomeninges give rise to an acute purulent meningitis. In infants the clinical course of illness is often rapid and is more often associated with diarrhoea and lesions in the gastro-intestinal tract than is the case with

older children and adults. However, just as in other forms of meningitis, the classical signs of meningeal irritation may be lacking in the infant and thus render the diagnosis more difficult. This was the case in our fourth patient where on admission there was nothing to indicate the presence of acute meningitis.

Age Incidence of Salmonella Meningitis. The age incidence of salmonella meningitis shows that there is a striking tendency for the very young to be affected. Table 1 shows the age distribution in 138 patients. This includes some of the patients reported by Henderson (1948) together with subsequent reports where the age group was available and including the four cases reported here.

TABLE 1
AGE INCIDENCE OF 138 CASES OF SALMONELLA MENINGITIS

Number of Cases	Age Groups				
	New-born	Less than 3 Months	3/12–1 Year	1–15 Years	15+ Years
138	55	31	26	14	12

The above figures show that 112 of the 138 cases (81%) occurred in infants under the age of 1 year and all but 12 occurred in children under the age of 15. The reason for this age distribution is not clearly apparent since the pathogenesis of salmonella meningitis is incompletely understood, but it is largely in keeping with certain other forms of meningitis such as the tuberculous and influenzal varieties. However, infection by salmonella organisms, where the clinical manifestations are confined to the gastro-intestinal tract, does not appear to be more common in children than in adults. It seems probable that the organism is carried to the meninges via the blood stream and it has been suggested that the high rate in infants is due to the preceding birth trauma rendering the tissues more susceptible to infection. This may be a factor in certain cases such as that reported by Neter (1944) where meningitis developed in a child aged three years who had had hydrocephalus since birth. Such a theory, however, does not explain the occurrence of outbreaks amongst newborn infants. In these it may be that certain inherent characteristics of the organisms themselves may be concerned in the localization in the meninges. It has also been suggested that salmonella infections of the meninges may follow other types of infection of the central nervous system due to a lowering of the local tissue resistance. In the 144 cases reviewed by Henderson (1948) five followed an attack of meningococcal meningitis and two others occurred during the course of treatment of syphilitic infections of the central nervous system. This hypothesis of decreased tissue resistance is one that is extremely difficult to prove or disprove. It is one which has been supported by Zinsser, Enders and Fothergill (1939) but it has lost much of its popularity in recent years. Neter (1944) has suggested that salmonella bacteraemia and meningitis may follow other types of infection such as otitis media, pyelitis and malaria. In our Case 1 the onset was preceded by an attack of whooping cough. It has also been suggested that the gastro-intestinal tract of the infant is more permeable to bacteria than that of the adult but again no satisfactory support for this hypothesis is available. One important factor is probably the well-known inability of the infant to produce a satisfactory antibody. Consequently, organisms gaining access to the blood stream are presumably in a more favourable position to reach the meninges and cause infection than in the adult where antibody formation is better.

Incidence of Various Salmonella Species. Table 2 shows the distribution of 151 salmonella species isolated from the cerebrospinal fluid and includes the four cases reported here in addition to those discussed by Henderson (1948). In addition to those shown in Table 2 the following species have been reported in isolated examples in the literature: *S. bovis-morbificans*, *S. bredeney*, *S. manhattan*, *S. paratyphi C*, *S. blegdam*, *S. montevideo* and *S. dublin*.

TABLE 2
SALMONELLA SPECIES IN 151 CASES OF SALMONELLA MENINGITIS

Salmonella Species	Number of Cases
S. paratyphi B	22
S. paratyphi A	7
S. enteritidis	45
S. cholerae-suis	8
S. typhi-murium	13
S. panama	17
S. havana	21
S. london	1
S. eastbourne	1
S. oranienburg	1
S. newport	2
S. anatum	1
S. derby	1
S. bareilly	1
S. loma-linda	1
S. new-brunswick	1
S. johannesburg	1
S. heidelberg	1
S. dublin	1
Undetermined	5

We have not included cases of meningitis due to *S. typhi* in this discussion. Although typhoid fever

is extremely common in this part of the world, where we have had experience of some 400 cases in the past few years, we have not yet seen a case of true typhoid meningitis. Many patients with typhoid fever present with signs of meningeal irritation but the cerebrospinal fluid is usually normal or shows only a very slight increase in the number of cells.

The distribution of salmonella types in Table 2 is probably not altogether accurate in certain respects. Up to 1935 only four salmonella species had been reported from the cerebrospinal fluid, namely, *S. paratyphi B*, *S. enteritidis*, *S. paratyphi A* and *S. cholerae-suis*. Lack of knowledge concerning the antigenic structure of the salmonella group would explain this failure to recognize other types. The increasing number of reports of salmonella species in the cerebrospinal fluid not previously identified makes it probable that any salmonella species, including many which are primarily pathogenic to animals, may localize in the meninges and cause meningitis.

Prognosis in Salmonella Meningitis. The death rate from this condition is high and particularly so in infants as compared with older children and adults. The introduction of broad spectrum antibiotics may materially alter the death rate in the future but so far experience with this form of treatment has been restricted by the small number of cases available. The incidence of sequelae is uncertain but is probably the same as that found in other forms of acute purulent meningitis. Table 3 below shows the number of deaths in relation to age group in a series of 143 cases where the age was known.

TABLE 3
NO. OF DEATHS RELATED TO AGE IN 143 CASES OF SALMONELLA MENINGITIS

Age	Number of Cases	Number of Deaths	Percentage Died
Newborn–30 days ..	67	63	94·0
30–90 days	20	17	85·0
90 days–1 year	26	23	88·4
1–15 years	18	12	66·6
15+years	12	9	75·0

The figures in certain of the age groups are too small to be significant statistically but if we consider the number of deaths in children over and under one year it will be seen that there were 21 deaths in 30 cases (70%) in the former group and 103 deaths in 113 cases (91%) in the latter age group. If we subject these results to analysis by the χ^2 test the probability (P) value for χ^2 is greater than 3·84 which indicates a significance difference between the death rates at the 5% level.

In addition to the association of deaths with age groups, the number of deaths in relation to the type of salmonella involved is of interest. Table 4 shows the number of deaths in 133 cases due to seven different salmonella species.

TABLE 4
NO. OF DEATHS RELATED TO SALMONELLA SPECIES IN 133 CASES OF SALMONELLA MENINGITIS

Salmonella Species	Number of Cases	Number of Deaths	Percentage Died
S. paratyphi B ..	22	13	59·0
S. paratyphi A ..	7	5	71·4
S. enteritidis ..	45	45	100·0
S. cholerae-suis ..	8	6	75·0
S. typhi-murium ..	13	13	100·0
S. panama	17	14	82·3
S. havana	21	21	100·0

All the cases of *S. enteritidis*, *S. typhi-murium* and *S. havana* infection proved fatal whereas as high a recovery rate as 41% is recorded in the 22 cases of *S. paratyphi B* infection. This finding does not seem to be related to age distribution since the number of cases in children under one year, due to *S. enteritidis*, is not statistically greater than those due to *S. paratyphi B*. Table 5 shows the relative age distribution of these two types of infection. It would appear that not all salmonella species have the same effect on the host though what factors may be responsible for the greater pathogenicity of some types as compared with others are at present unknown.

TABLE 5
DISTRIBUTION OF *S. PARATYPHI B* AND *S. ENTERITIDIS* WITH RESPECT TO AGE

Organism	Age Groups					Total
	Newborn–30 Days	30–90 Days	90 Days –1 Year	1–15 Years	15+ Years	
S. paratyphi B	6	6	3	3	3	21
S. enteritidis ..	13	8	14	7	2	44

Treatment of salmonella meningitis is at present unsatisfactory. Following the introduction of sulphonamides a number of cures were reported and recovery has also been attributed to the effect of streptomycin (Pearlman and Gordon, 1949). Padnos and Goldin (1951) also reported recovery in a case due to *S. bareilly* which was treated with intravenous aureomycin. Most salmonella strains are sensitive *in vitro* to the tetracycline drugs and they reach the cerebrospinal fluid in adequate amounts. It remains to be seen, however, whether they will effect a reduction in the mortality rate from this disease.

Summary

Four cases of meningitis due to salmonella infections are reported. Two of these were due to

salmonella strains not previously isolated from the cerebrospinal fluid, namely *S. johannesburg* and *S. heidelberg*.

Salmonella infections of the meninges occur most commonly in infants in whom there is a higher death rate than in adults or older children. Prognosis may depend on the type of salmonella responsible for the infection as well as the age group.

I wish to thank Dr. P. Klenerman, Paediatrician to King Edward VIII Hospital, for permission to quote from the case notes of the patients in her charge.

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CALCIFIED MESENTERIC LYMPHANGIOMA

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 2, 1957)

Levene, Walker and White (1956) reported two cases of mesenteric lymphangioma which presented as acute abdominal emergencies. They reviewed the published work, and showed that this is a rare condition. The following case is reported as an interesting complication of this disease.

Case Report

Paul R., aged 12, had from the age of 5 years recurrent attacks of central abdominal pain. These were accompanied by feelings of nausea and fullness in the epigastrium. The pain was colicky in nature, associated with constipation and relieved to some extent by the passage of flatus. At first the attacks occurred at intervals of five or six weeks, and they lasted for 24 hours. By the time he was 12 they had become less frequent but more severe, and vomiting occurred.

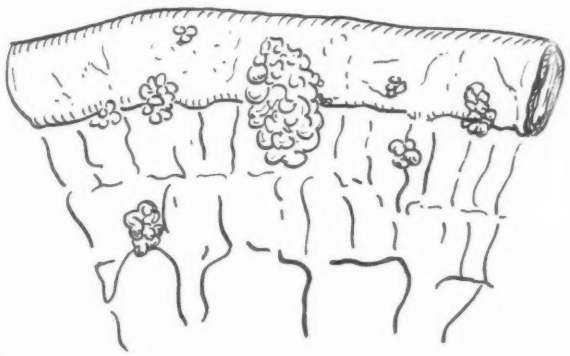

FIG. 2.—A portion of the jejunum seen at operation (about hal actual size).

FIG. 1.—Radiograph of the pelvis.

On examination of the abdomen there was no physical abnormality, but rectal examination revealed a large, mobile, spherical mass which could be balloted in the abdomen. The blood picture and urine were normal. A tuberculin test was negative. A radiograph showed a calcified mass in the pelvis (Fig. 1). A barium enema revealed no communication with the large bowel.

Laparotomy was undertaken (C.P.S.), and there was found to be a little cloudy fluid in the peritoneal cavity. The surface of the jejunum and most of the ileum showed extensive engorgement of the lymphatics, which in many places had formed collections of lymphatic cysts (Fig. 2). At the distal end of the ileum there was a large, round, hard mass lying in the mesentery, but attached to the bowel wall (Fig. 3). The tumour was excised together with 4 cm. of the ileum, and an end-to-end anastomosis was performed. In addition, a small nodule was taken from the mesentery for the purpose of histology. The patient made a good recovery. Three months later he was very well and had no abdominal pain or nausea.

Pathology Report (R.L.B.)

The mesenteric nodule was a fatty nodule 0·5 cm. in diameter and consisted of fibro-fatty tissue in which were many dilated lymphatic spaces. No other lesion was seen

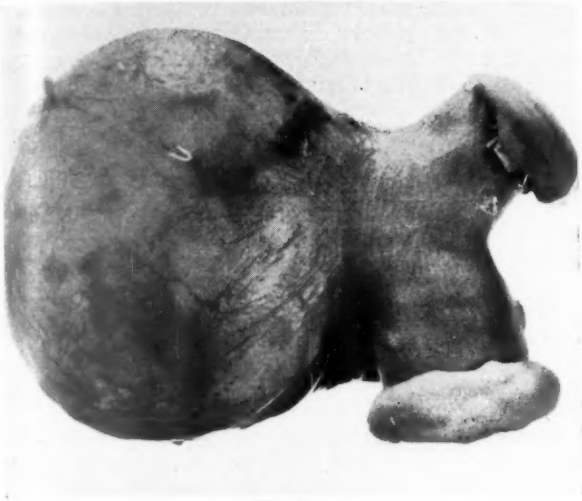

FIG. 3A.

FIG. 3B.

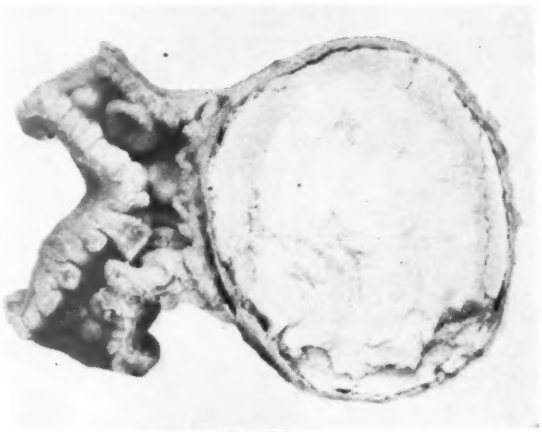

FIG. 3C.

FIG. 3.—A and B: Cyst and attached bowel. C: Cut surface of specimen showing polypoidal mucosa of small bowel (actual size).

FIG. 4.—Section of mesentery showing lymphangiectasis with some lymphoid aggregates (×120).

and the diagnosis was considered to be lymphangiectasis of the mesentery.

The main specimen was a segment of small intestine 4 cm. long with a spherical hard mass 4·5 cm. diameter attached just to one side of the mesenteric border. On bisection with the aid of a saw, the mass consisted of uniform cream necrotic material (resembling caseation) with a thin peripheral calcified shell. On the external surface of the tumour there were a few tiny transparent cysts containing clear fluid and measuring 1 mm. in diameter. The attached bowel showed two small polypoid lesions of the mucosa, but there was no ulceration. No lymph nodes were found in the mesentery.

The contents of the 'cyst' were necrotic and consisted of droplets of sudanophilic fat, much of it being birefringent. There was no iron pigmentation such as would be expected from old haemorrhage. The wall of the cyst consisted of dense fibrous tissue with some calcification; it had no connexion with the muscle of the bowel. In the mesentery there was a lymphangiectasis accompanied by a few small lymphoid aggregates (Fig. 4). The intestinal polypi showed a lymphangiectatic condition in the submucosa.

The final diagnosis was of mesenteric cyst with lymphangiectasis of the mesentery and small intestine.

Family History

No similar condition has been observed in any of the patient's relatives. About a year later his younger brother, aged 7, fell on a bar and ruptured his spleen. An operation to remove it became necessary and at the same time the bowel and mesentery were thoroughly examined. No signs of lymphangiectasis were seen.

Discussion

The nature of the attacks, the feeling of fullness and the relief from passing flatus, suggest that there was an element of subacute obstruction. Since the cyst has been removed there has been much improvement, and there are no symptoms referable to the condition. As a matter of interest a fat balance was carried out after the operation. This gave a normal result, with 91·5% absorption. The blood cholesterol level was 150 mm. %, and the total fatty acid 194 mg. %. It seems, therefore, that there is no interference with fat absorption.

This appears to be the first case recorded of calcification in a lymphangiectatic cyst.

We wish to thank Dr. K. Reeves, who referred the case, Mr. T. Schofield, F.R.C.S., for information about the patient's brother, Mr. N. Swain for the print of the radiograph and Mr. G. W. Griffin, F.I.M.L.T., for the photomicrograph.

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SWEAT TEST FOR THE DIAGNOSIS OF FIBROCYSTIC DISEASE OF THE PANCREAS

REPORT OF A FATALITY

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 8, 1957)

The recognition of the electrolyte disturbance in the sweat of patients with fibrocystic disease by Darling, diSant' Agnese, Perera and Andersen (1953) led Shwachman, Leubner and Catzel (1955) to devise a simplified method of obtaining sweat for biochemical assay.

In this method the patient is placed in a plastic bag up to the neck and covered with a blanket, the sweat being collected in a weighed square of gauze which is covered with a piece of impermeable sheeting and strapped to the back. The recommended time is 30-90 min., depending on the rate of sweating.

The test is now widely used. In spite of the theoretical risks no serious ill effects from it have been reported. We have had the unfortunate experience of a death following its use, which we record as a reminder of its potential danger.

Case Report

A boy, aged 13 months, was admitted to hospital on account of failure to thrive, backwardness and diarrhoea with bulky and offensive stools, for an unknown period. Delivery and the neonatal period had been normal but he sat up late, and was unable to get into a sitting position at the time of admission. He appeared in a neglected condition and the home conditions were bad. Apart from his low weight, flabby musculature and slight ichthyosis of the skin, physical examination revealed no abnormality.

The Wassermann reaction, chest radiograph and Mantoux test were negative, and the blood count was normal. The stools were pale, bulky, greasy and offensive; no pathogens were isolated. The duodenal fluid was slightly alkaline and showed tryptic activity to a titre of 1 : 32 (gelatin film method of Harrison, 1947). As this suggested pancreatic impairment, pancreatin granules were given with each meal. There was a rapid general improvement with increase in weight (5 lb. (2·25 g.) in four weeks) and he started to walk.

Although the child was now well, because of the apparent pancreatic impairment a Shwachman test was performed (after sedation with 1 ml. of paraldehyde) by the method described above but using hot water bottles to promote sweating. The test lasted two hours. The result, an increase in the weight of the gauze by 0·2 g., with complete absence of chloride and sodium, was equivocal, and it was decided to repeat the test a week later. The patient was sedated with chloral hydrate gr. 3 (0·05 g.) and, as this had no effect, paraldehyde 0·75 ml. As little sweat had been obtained in the previous test, the period of collection was extended to three hours under the same conditions as before. Throughout the patient's general condition appeared satisfactory, though on removal from the bag he appeared anxious and restless. This was attributed to the discomforts of the test. Half an hour later he vomited copiously. On examination then he was unconscious and pale with a hot, moist skin, and a temperature of 104° F. (40·3° C.) in the axilla. Respirations were irregular; pupils equal and reacting to light; deep reflexes normal. Under treatment with tepid sponging, subcutaneous and intravenous fluids and a mega unit of penicillin the temperature fell to 100° F. (37·6° C.) but the general condition deteriorated; the pupils became temporarily unequal and deep reflexes were absent. The pulse rate rose to 160-200 per minute. Death occurred in coma 14 hours after conclusion of the test.

Necropsy

This was performed five and a half hours after death and showed a well-developed boy with a somewhat rough skin, but without external abnormalities. Throughout the body there were scattered small and some larger flame-shaped haemorrhages mainly involving skeletal muscle and internal organs, especially marked on the pericardial and left septal surfaces of the heart, the omentum and the kidneys, and there were patches of haemorrhage in the well-pigmented adrenals. The lungs were uniformly and extremely congested, firm, and deep red. The gastro-intestinal tract, liver, bile passages, pancreas and ducts were macroscopically normal. The spleen

was slightly enlarged (45 g.), firm, and of a deep red with sharply demarcated large Malpighian corpuscles. Generalized mild but not abnormal lymphoid tissue hyperplasia was noted with enlarged tonsils and adenoids and a generalized mild lymphadenopathy. The thymus was normal (24 g.).

Examination of the skull showed the meninges tense but not congested, the brain bulging with flattened convolutions and a pressure cone of the cerebellum. A small grey nodule, 3-4 mm. in diameter, was noted projecting from the tuber cinereum close to the infundibulum to the left of the midline.

Sectioning of the brain (1,200 g.) showed dry, pale, bulging surfaces suggesting interstitial oedema. A small petechial haemorrhage was seen in the floor of the fourth ventricle. No further nodules were found.

Histology

Sections of the pancreas revealed no evidence of fibrocystic disease, and serial blocks of the terminal centimetre of the main duct showed no obstruction. The acinar cells were filled with secreting granules. The lungs showed extreme congestion only, with no abnormality of structure. The liver was normal apart from very scant round-cell infiltration of the portal tracts. Tonsils, cervical and abdominal lymph nodes, spleen and intestine confirmed slight generalized non-specific hyperplasia of the lymphoid tissue. No sign of an inflammatory reaction was seen in brain and meninges. Sections of cerebral cortex, corpus striatum and hypothalamus confirmed the oedema and showed a few small scattered capillary haemorrhages. The nodule on the tuber cinereum was a small lipoma of the pia mater. The abdominal skin showed hyperkeratosis, deficiency of the stratum granulosum and normal but inactive sweat glands (lumina closed).

Bacteriology

Films and cultures of the cerebrospinal fluid and spleen revealed no micro-organisms.

Pathological Summary

Heat stroke. Mild ichthyosis. Incidental finding: lipoma of meninges.

Comment

The necropsy findings, cerebral oedema and scattered body haemorrhages, taken in conjunction with the sequence of events, bears out the diagnosis of heat stroke, although the highest body temperature recorded, the first to be taken, and when the collapse had already occurred, was only 104° F. (40·3° C.) in the groin.

The method of obtaining sweat as devised by Shwachman is a simple and most useful diagnostic procedure but the potential danger of interference with the normal heat regulation of the body ought to be clearly recognized. At an external temperature of over 90° F. (32·2° C.) evaporation of sweat is almost the sole means of maintaining the normal body temperature (Best and Taylor, 1955). In the original experiments by Darling *et al.* (1953) a room heated to 90° F. was used to promote sweating, but in the Shwachman test the enclosure of the body by a plastic bag prevents any evaporation and permits a dangerous hyperpyrexia to occur. Patients with fibrocystic disease are known to sweat excessively and the danger of heat exhaustion due to excessive loss of electrolytes has been recorded by Kessler and Andersen (1951). This, however, need not be considered here as it bears no relation to hyperthermia. It is of interest though that the only fatality in their series occurred in an infant which was brought to the hospital during a heat wave wrapped up in a thick woollen blanket, thus preventing heat loss, and having a temperature of 106° F. (41° C.).

The simple screening test of Shwachman and Gahn (1956) which merely requires the placing of a hand on an agar plate incorporating silver chloride and an indicator, might be used more widely to demonstrate the increase of chloride in sweat of patients with fibrocystic disease. In its interpretation the possibility of a doubtful result ought to be borne in mind. We have found one false negative in a severely ill child in which fibrocystic disease of the pancreas was confirmed at necropsy. The polythene bag test should be limited to doubtful cases and when performed due regard must be given to the possibility of hyperthermia, and frequent recordings must be made of the body temperature. The duration of the test should be limited to the time specified by Shwachman and additional heat by hot water bottles or electric blankets should be avoided.

Summary

A fatality due to heat stroke following Shwachman's test involving the collection of sweat for the diagnosis of fibrocystic disease is reported. The potential danger of the test is emphasized.

We wish to thank Dr. C. G. Fagg at whose suggestion this case is being reported, Dr. H. Haber for his advice on the skin sections, and H.M. Coroner, Mr. J. H. Hoare, for permission to publish.

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PAEDIATRIC PATHOLOGY CLUB

Proceedings of the Third Annual Meeting

The third meeting of the Paediatric Pathology Club took place at the Children's Hospital, Sheffield, on November 8 and 9, 1957. Sixty members and guests attended.

Dinner was taken at the George Hotel, Hathersage, on the evening of Friday, November 8. There followed a discussion on pyelonephritis at which the principal speakers were W. W. Payne (London), R. C. B. Pugh (London), R. B. Zachary (Sheffield), A. M. MacDonald (Glasgow), B. I. Ivemark (Stockholm), K. B. Rogers (Birmingham), and A. G. Marshall (Wolverhampton).

The afternoon of Saturday, November 9, was taken up with a discussion of the National Perinatal Mortality Survey and a report by Dr. N. Brown on the pilot survey at Bristol.

Summaries of Original Papers

P. S. MacFarlane (Glasgow). 'Haemolytic Anaemia associated with Acute Renal Damage in Infancy.' Eight cases, in which a severe haemolytic anaemia was associated with renal damage, were described. The recent frequent association of what are rare diseases in infancy, may be of significance and the possibility that this is a new syndrome must be kept in mind.

The striking red cell morphology with frequent 'burr' cells was demonstrated.

Seven cases progressed to fatal uraemia in spite of adequate treatment of the haemolysis. At necropsy one case showed confluent cortical necrosis, five cases acute necrotizing glomerulitis and one case a severe tubular lesion with less severe glomerular damage. One case recovered.

This series suggests that the haemolytic anaemia does not cause the renal damage or *vice versa*, but rather that the two are concomitants and that a common ætiology is to be sought. The 'burr' cell phenomenon was present in two cases before a significant rise in blood urea had taken place.

There is no convincing evidence of an antigen-antibody reaction and the fundamental aetiology remains obscure.

R. C. B. Pugh (London). 'Pyelonephritis.' The term 'pyelitis' is probably unjustified as in nearly every case of so-called pyelitis there is also involvement of the renal parenchyma.

In a series of 150 necropsies in children, pyelonephritis was found in ten cases. Of these, six children had an underlying deformity of the urinary tract and in two cases pyelonephritis complicated tuberculosis.

An analysis of eight fatal cases of posterior urethral valves showed that in all there was pyelonephritis, which led to the development of renal rickets in two cases and to hypertension in the four older children.

When considering the morbid anatomical changes in pyelonephritis, the description of Weiss and Parker cannot be bettered, although a distinction should be made between the disease in neonates and in slightly older children, in whom the changes are very similar to those seen in adults.

The appearance of vascular lesions in pyelonephritis is also important especially as they resemble intrinsically those seen in hypertension. However, their distribution is different as they are confined to the scarred areas in pyelonephritis but occur in both the scarred and non-scarred areas in pyelonephritis complicated by hypertension.

The cases of glomerulonephritis, nephritis, pyelonephritis and nephrosis that occur in the neonatal period are a complex and as yet incompletely understood group.

N. O. Ericsson and B. I. Ivemark (Karolinska Institutet, Stockholm). 'Renal Dysplasia and Pyelonephritis in Infants and Children.' Clinical, radiological and pathological examinations were performed on 34 children, 30 of whom showed infections of the urinary tract. Eight were under 1 year of age, and 26 of them from 1 to 11 years. Malformations of the urinary tract predominated, 16 patients having ureterocele and nine ectopic ureters, an inevitable composition of paediatric material, as cases with no such malformations rarely undergo operation. Thirty-one females, and three males were encountered, a sex distribution due to the female predominance in pyelonephritis and ureteric malformations rather than in renal dysplasia. No preponderance of left-sided abnormalities was found.

The specimens were grouped in three categories. (1) *Dysplastic* (15 specimens) malformed kidneys with numerous primitive ducts resembling the mesonephric duct. Thirteen showed pyelonephritis. (2) *Presumably dysplastic* (16 specimens) mostly hydronephrotic kidneys with few medullary ducts ('medullary dysplasia') and primitive cortical 'ductules', resembling mesonephric ductules. All specimens displayed severe pyelonephritis. (3) *No obvious renal dysplasia* (three specimens). Ductules: no medullary dysplasia. Striking inflammatory changes.

The microscopic findings suggest abnormal budding of the ureter to be the underlying cause of the dysplasia. The cortical ductules described may be evidence of renal dysplasia—possibly residual mesonephric tubules or abnormal proliferation of ureteric buds. Concomitant

inflammation in all patients surviving more than seven days is an indication that renal dysplasia is an important predisposing element in the pyelonephritis of infancy and childhood.

C. G. PAINE (Sheffield). 'Changes in the Placenta with Particular Reference to Essential Hypertension and Pre-eclamptic Toxaemia.' A description of the normal ageing changes in placental tissue was given. This related to the villous stroma which was converted from primitive mesodermal tissue to adult fibrous tissue, the arterioles of the villous stalks which changed from primitive blood spaces to relatively thick, muscular walled tubes to deal with the increasing volume of foetal blood, the villous blood vessels with special reference to subtrophoblastic sinusoid formation in the late weeks of pregnancy, and the syncitiotrophoblast which started as a thick plastic multinuclear structure, and finished as a thin membrane capable of rapid metabolite exchange at full term. A description was given of the distribution of lipoid with normal syncitium.

The normal changes were compared with those seen in essential hypertension affecting pregnancy, and in pre-eclamptic toxaemia. In the former condition, thromboses and fibrin deposition in the overlying decidua were associated with local intervillous fibrin deposition and infarct formation, and with premature ageing of the villous blood vessels and stroma, such that subtrophoblast sinusoid formation was limited. In pre-eclamptic toxaemia, syncitial atrophy was accompanied by a diminution in lipoid. It was considered that this was related to the diminution in pregnandiol excretion which occurs in pre-eclamptic toxaemia.

J. BEVERLEY (Sheffield). 'Stress and Pathogenicity of Toxoplasma.' Evidence was produced that most toxoplasma infection in animals and humans remains subclinical. Instances from the literature of clinical grade infections in various species were cited to illustrate that such factors as cold, concomitant infections, captivity, infancy, pregnancy, injury and endocrine imbalances may have contributed to the severity.

A strain of toxoplasma, isolated from a rabbit, was found to be only feebly pathogenetic for non-pregnant mice, causing them to lose weight from the ninth to the 15th days after inoculation, but they completely recovered. When the same strain, in the same doses, was injected into other mice so that the peak of the illness occurred at different stages of pregnancy it was found that injection 11 to three days before pregnancy caused abortion with 17% of mothers dying; injection during the first 12 days of pregnancy caused abortion or full term still-births, or live births which soon died, and the maternal mortality was 55%; injection between the 13th and 16th day resulted in live litters which were not reared and no maternal mortality; and inoculation between the second and 12th day of lactation rarely caused neglect of the litters but a 92% maternal mortality around the time of weaning.

J. H. ALLAN (Sheffield). 'The Mineralization of Enamel in Developing Teeth.' Ground sections of human deciduous teeth, ranging in development from 26 weeks *in utero* to 18 months after birth, were examined in plane polarized light, and the following pattern of mineral accretion deduced.

1. Following the commencement of enamel organic matrix formation, a primary, fairly diffuse deposition of mineral matter occurs along a narrow zone at the incisal amelo-dentinal junction. From this latter area, the amount of mineral matter falls in a regular manner towards the periphery of the enamel.
2. In the peripheral enamel a secondary deposit then occurs, producing slightly better mineralized zones in the cervical region and just deep to the enamel surface. This secondary deposit results in an area of slightly lower mineral content being present in the centre of both labial and lingual enamel.
3. A final deposition then starts on the lingual side of the incisal amelo-dentinal junction and expands cervically and peripherally, gradually obliterating the primary and secondary deposition patterns. This final deposition, which initially advances parallel to the organic matrix incremental lines, gradually alters its direction until it is almost parallel to the enamel surface.

These results support the view that all the main phases of enamel mineralization proceed peripherally from the amelo-dentinal junction, not cervically from the incisal surface.

J. L. EMERY, G. H. JOWETT and MORAG S. MACDONALD (Sheffield). 'Post Natal Changes in the Glomeruli of the Kidney.' Kidneys from 235 children aged 26 weeks *in utero* to 13½ years were described.

The glomeruli were classified according to six stages of maturity. The percentages of these six stages were related to age.

A reproducibility survey showed that there had been a subconscious change in standards of classification during the period of the survey, but the following conclusions appear valid.

1. Primitive forms may persist until 4 to 6 months of age, but some of these may be abnormal.
2. The majority of glomeruli are of mature type from 6 years onwards, but it is not until after 12 years of age that all are of adult form.
3. A very wide individual variation in the rate of glomerular maturation was found.

In addition, various case reports were given.

BOOK REVIEWS

A Primer of Paediatrics. By ELCHON HINDEN; Foreword by K. H. Tallerman. (Pp. xv+356. 25s.) London: Macdonald. 1957.

This new book is designed for the senior student and family doctor and it is intended as an introduction to paediatrics.

There are three sections—from conception to 4 weeks of age, from 4 weeks to 2 years and from 2 years to puberty—and in each section both normal child care and children's diseases are considered. The subdivision into age groups thus clearly segregates neonatal paediatrics from, for example, the school health service, or prematurity from tuberculosis. The different subjects are discussed in a down-to-earth manner and the writing is in the first person; this, combined with the fact that there are no references to distract the attention, gives a comfortingly familiar style to the prose.

This book truly is an introduction to paediatrics and above all to paediatrics for the family doctor. It makes no excursions into controversy, it seeks no great scientific heights, nor is any subject dealt with very exhaustively. These are not the avowed purposes of the book, which is to act as a first presentation of paediatrics and in this object it can fairly be said to be successful. Throughout the text there is an abundance of sound commonsense views, sometimes expressed didactically, sometimes a little tenuous. The lack of an index will detract from its usefulness as a book to be consulted. For anyone about to start a study of paediatrics it can be wholeheartedly recommended as an introduction to what paediatrics is about. It is not a long book and every medical student starting his paediatric clerkship would benefit enormously if he were sent away for two or three days to read 'A Primer of Paediatrics' as though it were a novel. The text, which reads very easily, would make this a pleasure as well as instructive and would give a conception of paediatrics which no other book at present available is capable of doing.

Diabetes Mellitus: With Emphasis on Children and Young Adults. By T. S. DANOWSKI. (Pp. xxiv+510; illustrated. 108s.) London: Baillière, Tindall and Cox. 1957.

This book, according to the author, was originally intended to deal with diabetes in children, but it has been enlarged to embrace a presentation of the fundamental alterations in metabolism which occur in diabetes mellitus.

The first part is entitled 'Biochemical and Hormonal Aspects', and in the six chapters devoted to this section an attempt has been made to make a comprehensive survey of the main knowledge on carbohydrate metabolism and of the factors which affect it—hormonal, dietetic and experimental. The task the author has set himself is a very ambitious one and to condense all the relevant information into six chapters has necessitated a degree of condensing which makes it very hard reading. He includes, however, a considerable amount of literature for those who wish to go further into the matter.

The next part deals with 'Manifestations, Diagnosis and Therapy' and here the author varies between recounting the experiences gained from his own clinic and that culled from the enormous literature already existing on diabetes. The first chapters of this, on incidence, type of onset, heredity, the methods to be adopted in making the diagnosis, etc., are excellent. The following chapters, however, to some extent go over the same ground as has already been covered in Part 1 and he again discusses the question of how insulin acts, what happens when glucose is given, the effects of glucagon, epinephrine, etc., and one feels that these chapters could have been very much shortened with considerable advantage. When dealing with the actual therapy, the author attempts to adopt a mid-way position between the ultra-strict school of treatment and those who allegedly adopt a 'laissez faire' method of treatment. The reviewer found it rather difficult to appreciate exactly where the author stood in this matter. However, it is quite obvious that it is impossible to write a description of a therapy which has to vary with each patient, and it is probable that many apparent differences between different methods of treatment are largely non-existent in actual fact. He finishes this section with a chapter on the regulation of hydrogen ion concentration of body fluids, which seems quite out of place.

Part 3, entitled 'Developmental Aspects and Complications', merely continues the story of the treatment of diabetes. The first chapter deals with such matters as diabetic acidosis and coma and the various factors that cause them, the symptomatology and a theoretical discussion of the methods of treatment. The next chapter once again discusses the various factors, such as the metabolism of sugar which may lead to ketosis, and for a third time discusses the adrenocortical system, electrolytes, *p*H, etc. It is only in the following chapter that the actual treatment is dealt with. Again in these three chapters, there is considerable repetition of previous work and in the reviewer's opinion, they could well be condensed into one chapter.

The next two chapters deal with somatic growth and development of the juvenile diabetic—personality, emotions and scholastic performance, etc. These are unfortunately relatively short chapters and the reviewer would have liked to have had a rather fuller account of the author's own experiences in his clinic as well as the well-documented summaries that he gives of the literature. The next chapter deals with the vascular, ocular and renal changes and only 13 pages are devoted to this in a book which contains nearly 500 pages. As this particular problem is the one which looms most menacingly over the adolescent diabetic, it is disappointing that a much fuller treatment of this subject is not given.

The final chapters deal with the gastro-intestinal tract and liver, fertility and pregnancy, and a final short one on

neuropathy, insulinogenic lipodystrophy and necrobiosis lipoidica in diabetics.

In the reviewer's opinion, the very praiseworthy attempt of the author to combine the physiological, experimental and clinical approaches to diabetes into one book has been only a partial success. It has made the book rather difficult to read, and for those who are rather more interested in the clinical aspects of diabetes in children, much of the book is unrewarding. The clinical sections of the book are somewhat uneven, but on the whole are good, and one of the best aspects of this book is the excellent bibliographies which are given at the end of each chapter. The book is well presented and there are only a few typographical errors. There is an excellent table of contents and a good index.

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, 2nd ed. By LAWSON WILKINS. (Pp. xxvi+526; illustrated. £6 12s. 6d.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

This book, first published in 1950, was quickly and universally recognized as a classic text. Endocrine disorders, apart from cretinism and diabetes, are rare in childhood and only a specialist working in a great city with the resources of a famous general hospital around him could have studied adequately the natural history of endocrine disease in childhood. When Lawson Wilkins started his endocrine clinic at the Harriet Lane Home nearly 20 years ago endocrinology was practically limited to observational records, and, as chemistry, physics and biology made their astonishing contributions, Wilkins was ready to apply these new methods to endocrine disease in childhood. In this second edition of his fine textbook he generously acknowledges the work of the 17 associates who have worked with him from 1938 until today. To read this list of distinguished names is to recognize how much fundamental work in endocrinology he has inspired and sponsored. Not included in the list of associates are Money and the two Hampsons, who at his instance, have made important psycho-sexual studies which are fully described in the new edition. Their fundamental conclusion is that the sex rearing (up to 2 years), and not gonadal, hormonal or chromosomal sex, determines the psycho-sexual orientation and that to change the sex of rearing is an invitation to disaster. In those fields in which the author is most interested this edition is not only up to the minute, but a little in advance of Greenwich mean time. It includes, for example, important discussions of the mental prognosis in hypothyroidism (Smith, D. W., Blizzard, R. M. and Wilkins, L., *Pediatrics*, 1957, **19**, 1011) and the sex chromatin pattern in testicular disorders (Grumbach, M. D., Blanc, W. A. and Engle, E. T., *J. clin. Endocrinol. Metab.*, 1957, **17**, 703) which have just reached the library tables in this country.

This edition is larger by 140 pages than the first edition, but it retains the same splendid factual and pictorial quality. The chapter on diagnostic methods has been rewritten and is now a comprehensive summary of the available techniques, though English readers will regret that there is no mention of Norymberski's 17-ketogenic assay which is still giving good service in laboratories here. Methods of investigation of thyroid function are excluded from this chapter and it might save space in future editions if the whole of this chapter were broken up and redistributed. There is some repetition of information; for example, the effect of A.C.T.H. on the output of steroids in adreno-cortical hyperplasia is given three times on pages 69, 305 and 333. With the multiplication of new methods there will be an opportunity in the next edition for a division of available diagnostic techniques into categories—essential, useful and research. There is no discussion as to whether I^{131} should be used in young children, a matter which has occupied British workers (*Arch. Dis. Childh.*, 1956, **32**, 166). The 80 pages devoted to the thyroid is the best account of thyroid disease in children in any textbook. The author gives good evidence for his belief that the mental and neurological deviations in cretinism are the direct result of thyroxine deficiency and not due to an associated congenital defect. In the treatment of thyrotoxicosis in childhood, preference is given to the use of anti-thyroid drugs rather than to surgery. Generous reference is made to papers by British authors (both in this section and throughout the book), but there is no mention of the observation of P. R. Evans (*Pediatrics*, 1952, **41**, 706) on the vertebral changes in hypothyroidism. Paediatricians will turn eagerly to the account of adrenocortical hyperplasia, for most of the dramatic advances in this field have been the work of the author and his associates. In the maintenance treatment of congenital virilism he recommends 25-75 mg. of intramuscular cortisone every third day and two to five DCA pellets of 125 mg. each by implant in the salt-losing type with the addition of 2 to 3 g. of sodium chloride daily. The need to watch height increments in these children as well as 17-ketosteroid output is emphasized.

Dwarfism and the problems of disturbed growth are still in the observational stage, and they will remain static subjects until growth-hormone assays are possible in man, so there is little that is new to be related here. The author has retained the same height standards as in the first edition which, adapted from Engelbach's tables of 25 years ago, are now 1 to 3 in. below the 50 percentiles in children over the age of 5 years in the most recent and reliable surveys. The chapters on calcium and phosphorus metabolism and on carbohydrate metabolism have been largely rewritten and are now worthy of the rest of the work. All readers will be grateful for two lucid chapters on deficiencies and deviations of sexual development—a subject made more confusing by the method of chromosomal sexing devised by Barr. The genetic explanations of these disorders are not yet complete, but the author produces a series of satisfactory hypotheses which are consistent with the known facts.

This book is essential reading for paediatricians, for there is much information here collected which cannot easily be discovered elsewhere. Lawson Wilkins' work has added lustre to the great traditions of the Johns Hopkins Hospital.

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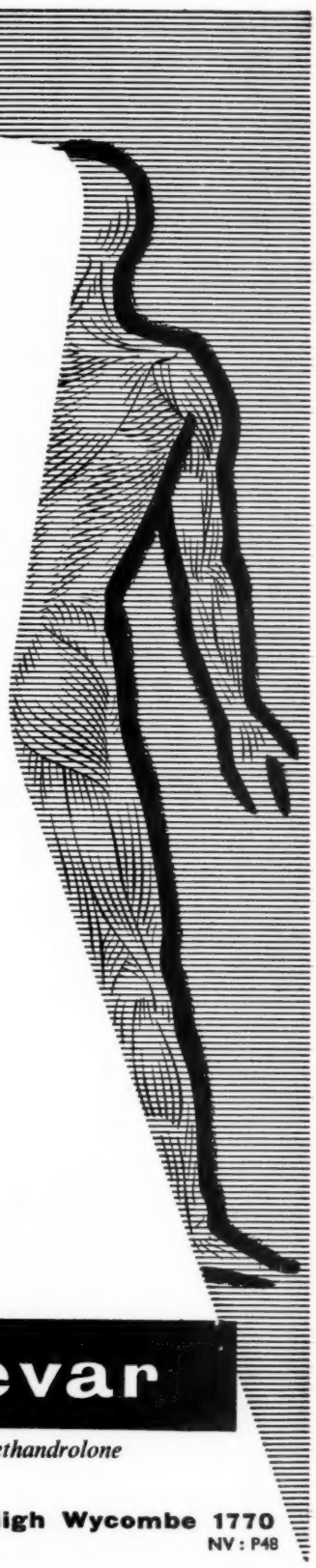

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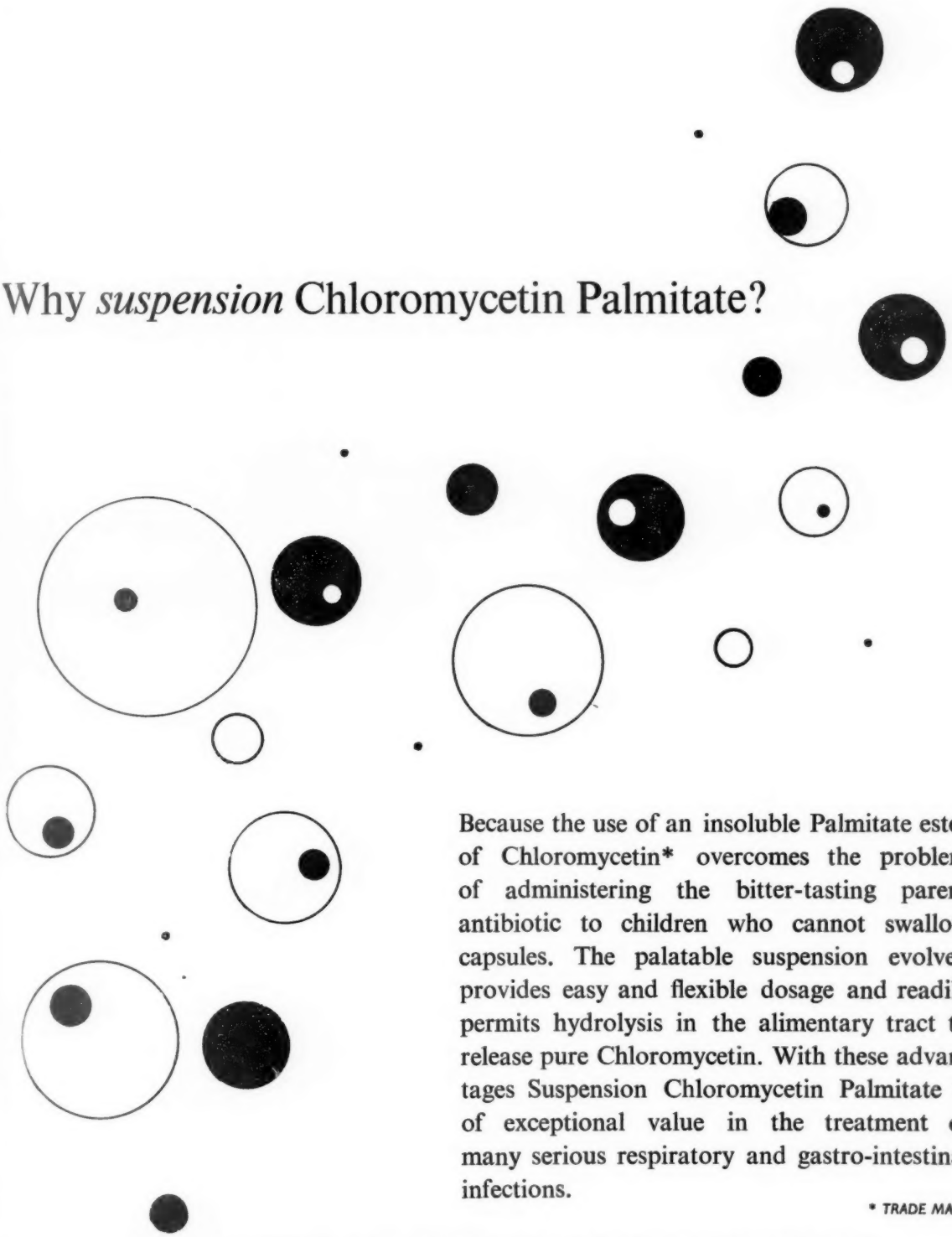

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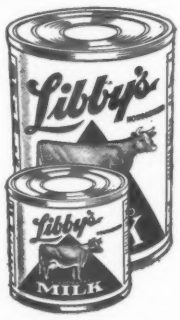

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